Gordis Epidemiology

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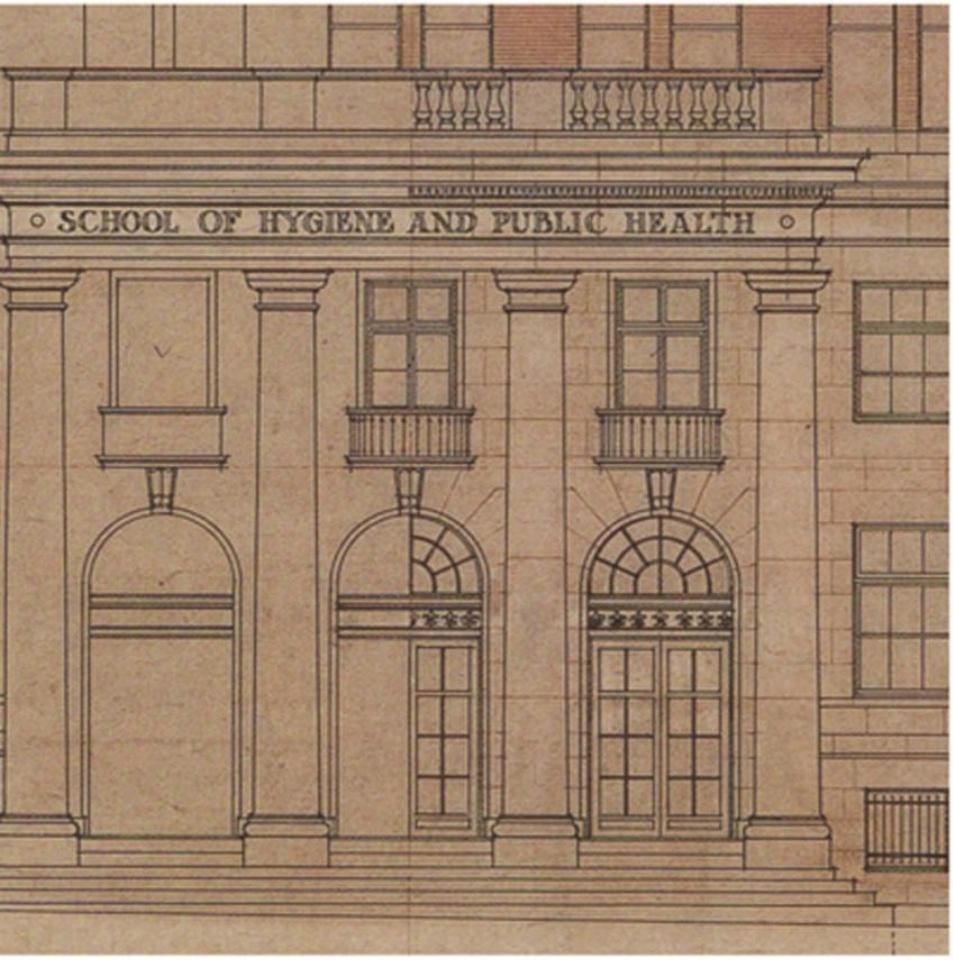

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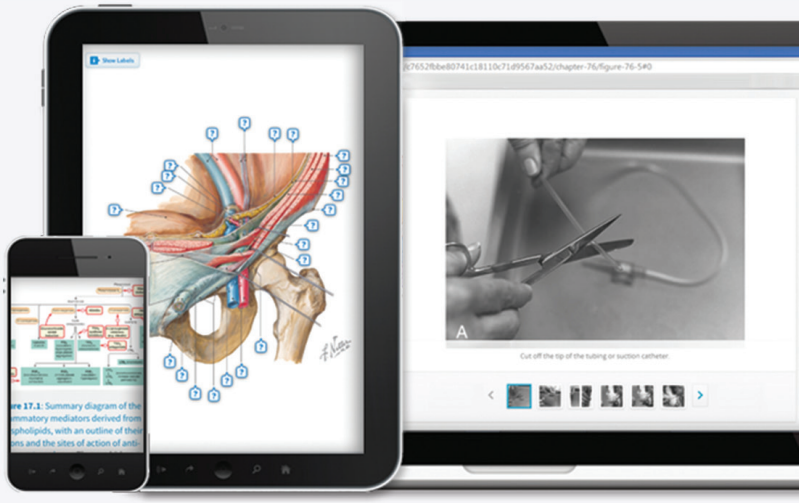

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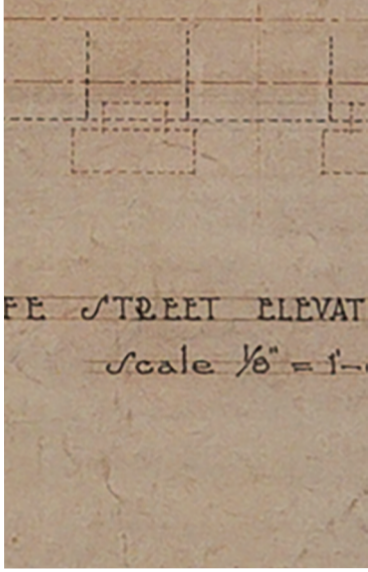

DAVID CELENTANO, ScD, MHS
Dr. Charles Armstrong Chair and Professor
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

MOYSES SZKLO, MD, MPH, DrPH
University Distinguished Professor
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

YOUSSEF M.K. FARAG, MD, PhD, MPH
Associate Faculty
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

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Elsevier
1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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PREFACE

Epidemiology is the foundational discipline underlying public health. Clinical research relies heavily on epidemiologic concepts and methods, and contemporary medical care and health services research, particularly relevant in comparative effectiveness studies and statistical approaches to "big data" (as in the use of the electronic medical record for health studies). As Dr. Leon Gordis wrote in his preface to the fifth edition, "*Epidemiology is the basic science of disease prevention and plays major roles in developing and evaluating public policy relating to health and to social and legal issues*." There are many uses of epidemiology today. Much epidemiologic research focuses on establishing etiologic associations between putative risks and health outcomes. However, epidemiology is also widely used in the evaluation of primary and secondary prevention programs, comparisons of interventions, and the evaluation of policy at the population level. Epidemiologic findings commonly find their way into public media, providing the public and policy makers with data to guide personal decisions regarding their behavior. Think about the SARS-CoV-19 pandemic that swept the world in 2020–2021. The scrutiny focused on epidemiology may cause researchers and practitioners some discomfort, as the interpretation of basic epidemiologic principles can be subject to considerable error. In the contemporary anti-science rhetoric surrounding COVID-19, epidemiology has become a household name while at the same time being derided by some segments of society. Our task in this book is to make the thinking underlying epidemiology transparent.

This text is intended to be a basic introduction to the definitions, logic, and use of epidemiologic concepts and methods to elucidate factors influencing health and disease. We have tried to illustrate the principles with contemporary and historical examples of how epidemiology is applied in the real world. The examples selected include both "classic examples" from the early days of the development of the discipline of epidemiology and contemporary examples such as COVID-19 and monkeypox. Where appropriate, we draw on examples pertaining to clinical practice or health policy.

Upon the passing of Dr. Gordis in 2015, the sixth edition of this book has been revised by two new authors, both of whom worked with and under Professor Gordis and have been actively engaged in teaching epidemiology at Johns Hopkins for over four decades. We have generally retained the structure and organization of the previous edition in this seventh edition. In the fifth edition, learning objectives were inserted in most chapters, and we have revised these and updated the examples throughout. Additional new review questions have been added to most chapters. A significant change in the sixth edition was a reversal of the order of the methods in epidemiology that were previously presented at the end of Section I and more extensively in Section II. Rather than leading with the randomized trial (or the "experimental" design) and then comparing observational study design to the gold standard, we have organized the presentation of epidemiologic methods along a study continuum from clinical observation to case-series to the use of ecologic studies and then to cross-sectional investigations as the foundational approach to epidemiologic hypothesis development. We then follow with case-control and cohort designs, leading up to the randomized trial. This more organically follows the development, in our opinion, of how epidemiologic observations and hypotheses are developed in the daily practice of *doing* epidemiology.

As with the previous edition, the seventh edition consists of three sections. Section I addresses how epidemiology is used to understand health and the development of diseases in populations as the basis for interventions to influence the natural history of disease. The first six chapters provide the conceptual framework underlying the discipline of epidemiology and present many of the basic principles of the discipline. Chapter 1 provides an overview of epidemiology, using many historical examples to illustrate how the field developed in historic context. Chapter 2 is concerned with how disease is transmitted in populations, both directly (in the case of infectious pathogens) and indirectly (for example, through a vector such as a mosquito or contaminated air). The basic terms used in epidemics are presented and illustrated to guide the student in seeing how

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these principles and terms are used. Chapter 3 addresses disease surveillance and how we measure morbidity in populations, while Chapter 4 is concerned with aspects of mortality and measures of disease impact in populations. Chapter 5 focuses on ways to detect disease in populations, comparing different approaches to differentiate people who have a disease from those who are disease free, articulating how screening tests can be adjusted to better diagnose those with or those without the disease in question. The issues of the reliability and validity of screening tests are of critical interest to both clinicians and to those planning for health services. Finally, Chapter 6 presents how the natural history of disease can be used to best express disease prognosis, using examples of case-fatality and survivorship.

Section II details the methods used by epidemiologists primarily to ascribe associations between a hypothesized exposure (risk) and a health outcome. Chapter 7 discusses the initial observations made in clinical practice (the case report) leading to a recognition of an accumulation of cases that appear to have some commonalities (the case series). This is followed by an introduction to the ecologic design and its analysis, with cautions as to its interpretation. Finally, cross-sectional (snapshot) studies are presented as the groundwork for hypothesis development. Chapter 8 then introduces observational studies as commonly used in epidemiology, addressing case-control and cohort studies, which are then compared in Chapter 9. To this point, we are addressing exposures as they occur in populations, where we are observers of exposures and their putative impacts on health outcomes. In Chapter 10 we move to the "experimental" approach (randomized trial) in which the investigator "assigns" exposure or health intervention—generally randomly—to study participants to address how this influences the health outcome. In this case the exposure is under the control of the investigator, not the study participant, a crucial difference in the randomized trial as compared to the cohort or other observational study design. Chapter 11 discusses a series of issues involved in the conduct of randomized trials, including sample size, power, and generalizability; determining efficacy (vs. effectiveness); ethical considerations; and the US Federal Drug Administration phases for evaluating new drugs. We added new content in Chapter 11 to describe the context, design, and implications of landmark historical clinical trials. In Chapter 12 we present issues on estimating risk, including absolute and relative risk and their interpretation, calculating and interpreting an odds ratio in a case-control study and in a cohort study, and doing so in a matched-pairs case-control study. In Chapter 13 the concept of risk is expanded to include the calculation and interpretation of the attributable risk, the population attributable risks, and their use in evaluating the success of prevention programs. Causal inference is introduced in Chapter 14 and focuses on how to derive inferences in epidemiologic investigations. Chapter 15 presents issues of bias, confounding, and interaction in epidemiologic studies and discusses how they influence causal inference. Finally, Chapter 16, extensively updated for the seventh edition, addresses the role of genetic and environmental contributions to the etiology of disease and presents new methods of genetic research commonly used in epidemiologic studies today. We also present the amazing growth in genomics research in the past dozen years, and have added a glossary of genetic epidemiology terms to provide the student with some guidance for this somewhat complex field.

Section III addresses the uses of epidemiology in everyday public health. The final four chapters address some of the critical issues facing the field today. Chapter 17 illustrates how epidemiologic principles and designs described in Sections I and II are used in the evaluation of health services. Chapter 18 addresses the use of epidemiology to evaluate screening programs, while Chapter 19 details how epidemiology can be used to address major areas of public health policy. The final chapter summarizes ethical issues confronted in the practice of epidemiology and reviews some of the important professional issues confronted by the field today.

We have continued Professor Gordis' use of illustrations and examples to demonstrate how epidemiologic issues and principles are put into practice. We have updated examples extensively and added new examples throughout the text. Many of the prior chapters have been extensively edited and updated, with some chapters greatly expanded.

Our aim for this book is to allow the reader to appreciate how epidemiology can be used to respond to population health problems confronting society today. Our expectation is not that the reader will be able to conduct an epidemiologic investigation after reviewing this text. Rather, we hope that there will be an appreciation of what epidemiology is, how and why we use basic research and evaluation designs, and how to interpret the

basic findings of an epidemiologic study. We hope that the excitement we feel about the uses of epidemiology will come across to the reader of this text. It took a pandemic for the world to recognize the critical role of epidemiology in our lives!

The cover illustration selected for this edition of *Gordis Epidemiology* has special meaning. The cover is the original architectural rendering of the building supported by the Rockefeller Foundation where the Johns Hopkins School of Hygiene and Public Health was originally housed. Today we continue to inhabit this edifice, where the roots of modern epidemiology developed. While our building today is massively built out, this symbol of the first home of our faculty is sentimental to us where all the authors of this book obtained their doctoral training in public health and epidemiology.

David Celentano
Moyses Szklo
Youssef M.K. Farag
August 2023

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ACKNOWLEDGMENTS

This book reflects the contributions of generations of teachers of epidemiology at Johns Hopkins, first as the School of Hygiene and Public Health with its first class in 1919, and more recently as the Bloomberg School of Public Health. The course was developed by the Department of Epidemiology faculty and was first taught as Principles of Epidemiology by Dr. Abraham Lilienfeld, the chair of the department from 1970 to 1975. Dr. Leon Gordis became the course instructor following an acute illness experienced by Dr. Lilienfeld in the midst of teaching the subject in 1974. Dr. Gordis then was the primary lecturer for the following 30 years. In addition, Dr. Gordis taught epidemiology to cohorts of School of Medicine students at Johns Hopkins at the same time. This book was developed from these experiences, and Dr. Gordis was the sole author of the first five editions of this popular text.

The current authors were all trained in public health and epidemiology at Johns Hopkins and were actively engaged as members of the epidemiology teaching team for many years when they were junior faculty. Dr. Szklo taught the second course in the epidemiology sequence, Intermediate Epidemiology. Upon Jon Samet's departure to University of Southern California in 2008, Dr. Celentano became the chair of the Department of Epidemiology, and the director of Principles of Epidemiology course, which has recently been revised in content and renamed Epidemiologic Inference in Public Health 1. Its content reflects this seventh edition of *Gordis Epidemiology.*

With this edition, we welcome Dr. Youssef M.K. Farag as an author. In the sixth edition, Dr. Farag worked diligently with us in obtaining updated materials, new examples, a thorough review of everything we wrote, and rewriting entire new sections. Dr. Farag is a physician and an epidemiologist. He received his medical degree from Mansoura University Faculty of Medicine in Egypt, and completed his clinical internship in Mansoura University Hospitals, as well as Harvard Medical School affiliated hospitals. He completed a postdoctoral research fellowship at Harvard Medical School, and has an MPH and a PhD in epidemiology from our department at Johns Hopkins Bloomberg School of Public Health where he was recognized by students and faculty and received awards as a gifted teacher of epidemiology over several years. He has richly earned his place on the masthead of this seventh edition!

Many colleagues have made invaluable contributions to this revision of *Gordis Epidemiology.* Chief among them was the late Dr. George W. Comstock, mentor, adviser, and sage scientist to both Drs. Celentano and Szklo. We also acknowledge the assistance of many past and current colleagues, including Haroutune Armenian, our former chair; Jonathan Samet; and Michel Ibrahim, who joined us as professor following his 2002 retirement as dean at the University of North Carolina–Chapel Hill. Others who have had major impacts on the teaching program in the department include Javier Nieto, Rosa Crum, Paul Whelton, Stephen Gange, Shruti Mehta, and Alvaro Munoz. Among prior co-instructors of the introductory course we acknowledge Bill Moss, Elizabeth Platz, Jennifer Deal, and Pablo Martinez Amezcua for their dedication to educating scores of public health students in the "art" of epidemiology. In particular, Dr. Deal has made outstanding contributions to our introductory course, and many of the examples in this edition come from her suggestions. The support of many deans of the school is also appreciated, including the late D.A. Henderson, Al Sommer, Mike Klag, and Ellen MacKenzie. The course on which this book is based would not exist without the long-term dedication and knowledge of our colleague Allyn Arnold who served as the bridge from the Gordis years to the present.

Preparing the seventh edition of this book was a significant undertaking for us. Our goal was to preserve Dr. Gordis' voice—and humor—and to retain the style of the text as much as possible. We also sought to update examples and to intersperse new illustrations of the epidemiologic principles we are presenting along with time-honored classics that were included in earlier editions. Clearly the COVID-19 epidemic gripping the world made clear many of these principles.

The chapter on the role of genetics in contemporary epidemiology was heavily influenced by our genetic epidemiology colleagues Priya Duggal and Genevieve Wojcik. This field has been changing so rapidly—and is

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so technologically complicated to the naïve—that they assisted us in doing a major revision in this seventh edition. We cannot thank them enough for their contributions to this chapter.

Preparing the seventh edition of *Gordis Epidemiology* has brought us many memories of Leon and his legacy at Johns Hopkins. The department has certainly changed since he stepped down as chair in 1993. Today we are a significantly larger faculty, numbering 135 full-time faculty in 2022, covering many more areas of epidemiology in greater depth in which there are eight different educational tracks, in addition to a new program in pharmacoepidemiology, and using tools unimaginable even a decade ago. At the same time, the discipline remains grounded in the ideas originally set forth by Wade Hampton Frost at the dawn of our school in 1919. This book is a testament to the thought-leaders and giants of epidemiology who have studied and taught epidemiology at Johns Hopkins over the past 100 years and hopefully will guide us into our second century of practice, education, research, and service.

David Celentano
Moyses Szklo
Youssef M.K. Farag
August 2023

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1

Introduction

I hate definitions.

—Benjamin Disraeli (1804–1881, British Prime Minister 1868 and 1874–1880)

WHAT IS EPIDEMIOLOGY?

Epidemiology is the study of how diseases or health characteristics are distributed in populations and the factors that influence or determine this distribution. Why does a disease develop in some people and not in others? The premise underlying epidemiology is that disease, illness, ill health, and excellent health status are not randomly distributed in human populations. Rather, each of us has certain characteristics that predispose us to, or protect us against, a variety of different diseases. These characteristics may be primarily genetic in origin, the result of exposure to certain environmental hazards, or the behaviors (good and bad) that we engage in. Perhaps most often, we are dealing with an interaction of genetic, environmental, and behavioral and social factors in the development of disease.

A broader definition of epidemiology than that given previously has been widely accepted. It defines epidemiology as "*the study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems.*"[1] What is noteworthy about this definition is that it includes both a description of the content of the discipline and why epidemiologic investigations are carried out.

Perhaps it is best to go back to the roots of the discipline. Wade Hampton Frost, the inaugural chair of the Department of Epidemiology at the Johns Hopkins School of Hygiene and Public Health. Frost wrote:

> *"For epidemiological description the unit is an aggregation of individuals making up a population, and description of the mass-phenomenon of a disease consists of its types and frequency of occurrence in the population as a whole and in its different component groups."*[2]

This statement was to contrast with the clinical description of disease where "*the unit is an individual, and the phenomenon of the clinical reaction may be described in terms of the character and distribution of anatomic lesions and the nature and sequence of symptoms.*"[2]

OBJECTIVES OF EPIDEMIOLOGY

What are the specific objectives of epidemiology? First, to identify the *etiology,* or *cause,* of a disease and its relevant risk factors (i.e., factors that increase a person's risk for a disease). We want to know how the disease is transmitted from one person to another or from a nonhuman reservoir to a human population or why it arises due to risk behaviors the person engages in. Our aim is to intervene to reduce morbidity and mortality from the disease. We want to develop a rational basis for prevention programs. If we can identify the etiologic or causal factors for disease and reduce or eliminate exposure to those factors, we can develop prevention programs. In addition, we can develop appropriate vaccines and treatments, which can prevent the transmission of the disease to others. However, while we may not always be able to identify *a cause* of a disease, epidemiology can be used to identify the *factors associated with*, but not necessarily causing, the disease. For example, Black individuals are more likely to develop hypertension. The Black race, however, is not causally related to hypertension; this relationship is explained by numerous causes for hypertension that are more common among Black persons, such as obesity and salt intake, which explain

the association. It is, however, useful to know about this noncausal relationship because it allows us to define Black individuals as a high-risk group for hypertension, which should be primarily targeted by preventive programs aimed at reducing associated causes.

The second objective of epidemiology is to determine the *extent of disease* found in the community. What is the burden of disease in the community? This question is critical for planning health services and facilities and for estimating how many future health care providers should be trained.

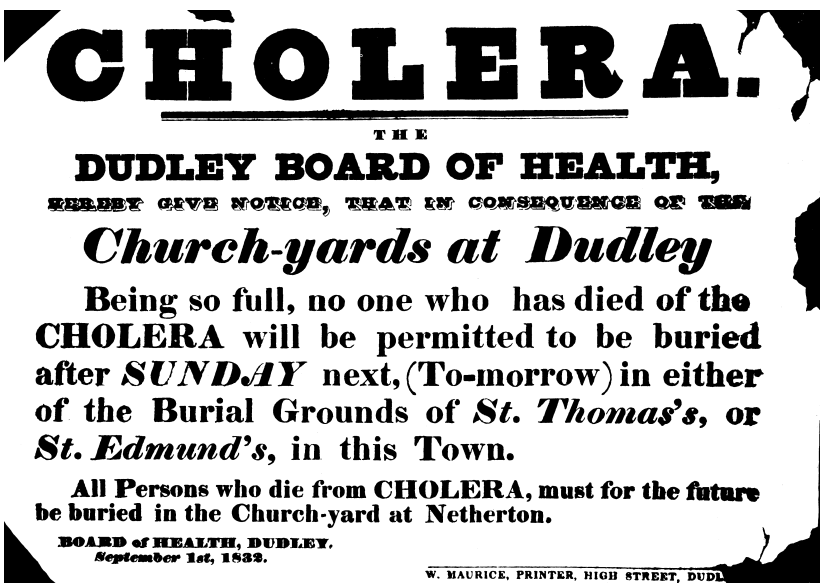
A third objective is to study the *natural history and prognosis of disease*. Clearly, certain diseases are more severe than others; some may be rapidly lethal, whereas others may have extended durations of survival. Many diseases are not fatal, but may affect quality of life or be associated with disability. We want to define the baseline natural history of a disease in quantitative terms so that as we develop new modes of intervention, through programs to prevent the onset of disease, through treatments, or through new ways of preventing complications, we can compare the results of using these new modalities with the baseline data to determine whether our new approaches have truly been effective.

Fourth, we use epidemiology to evaluate both *existing and newly developed preventive and therapeutic measures and modes of health care delivery*. For example, does screening men for prostate cancer using the prostate-specific antigen (PSA) test improve mortality in people found to have prostate cancer? Has the growth of managed care and other new systems of health care delivery and extension of health care insurance had an impact on the health outcomes of those involved and on their quality of life? If so, what has been the nature of this impact and how can it be measured?

Finally, epidemiology can provide the foundation for *developing public policy* relating to environmental problems, genetic issues, and other social and behavioral considerations regarding disease prevention and health promotion. For example, is the electromagnetic radiation that is emitted by cell phones, electric blankets and heating pads, and other household appliances a hazard to human health? Are high levels of atmospheric ozone or particulate matter a cause of adverse acute or chronic health effects in human populations? Is radon in homes a significant risk to human beings? Which occupations are associated with increased risks of disease in workers, and what types of regulation are required to reduce these risks?

Changing Patterns of Community Health Problems

A major role of epidemiology is to provide clues to changes that take place over time in the health problems presenting in the community. Fig. 1.1 shows a sign in a


CHOLERA!

THE

DUDLEY BOARD OF HEALTH,

HEREBY GIVE NOTICE, THAT IN CONSEQUENCE OF THE

Church-yards at Dudley

Being so full, no one who has died of the CHOLERA will be permitted to be buried after *SUNDAY* next, (To-morrow) in either of the Burial Grounds of *St. Thomas's*, or *St. Edmund's*, in this Town.

All Persons who die from CHOLERA, must for the future be buried in the Church-yard at Netherton.

BOARD of HEALTH, DUDLEY.
September 1st, 1832.

W. MAURICE, PRINTER, HIGH STREET, DUDL

Fig. 1.1 Sign in cemetery in Dudley, England, in 1839. (From the Dudley Public Library, Dudley, England.)

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cemetery in Dudley, England, in 1839. At that time, cholera was the major cause of death in England; the churchyard was so full that no burials of persons who died of cholera would henceforth be permitted. The sign conveys an idea of the importance of cholera in the public's consciousness and in the spectrum of public health problems in the early 19th century. Clearly, cholera is no longer a major problem in the United States today, but in many low-income and war-torn countries of the world it remains a serious threat, with many countries periodically reporting outbreaks of cholera that are characterized by high death rates, especially in children, often as a result of inadequate or inaccessible medical care and, ultimately, clean sources of water.

Let us compare the major causes of death in the United States in 2019 and 2020 (Fig. 1.2). The categories of causes have been color coded as described in the caption for this figure. In 1900 the leading causes of death were pneumonia and influenza, followed by tuberculosis and diarrhea and enteritis. In 2020 the leading causes of death were heart disease, cancer, coronavirus disease 2019 (SARS Co-V-2), and unintentional injuries.[3] What change has occurred? During the 20th century there was a dramatic shift in the causes of death in the United States. In 1900 the three leading causes of death were infectious diseases; however, now we are dealing with chronic diseases that in most situations are not communicable or largely infectious in origin. Consequently, the kinds of research, intervention, and services we need today differ from those that were needed in the United States in 1900.

The pattern of disease occurrence currently seen in some developing countries is often similar to that which was seen in the United States in 1900: infectious diseases remain the leading causes of death.[4] However, as countries become industrialized, they increasingly manifest the mortality patterns currently seen in developed countries, with mortality from nontransmissible chronic diseases becoming the major challenge (this is commonly referred to as the "epidemiologic transition"). However, even in industrialized countries, as human immunodeficiency virus (HIV) infection and

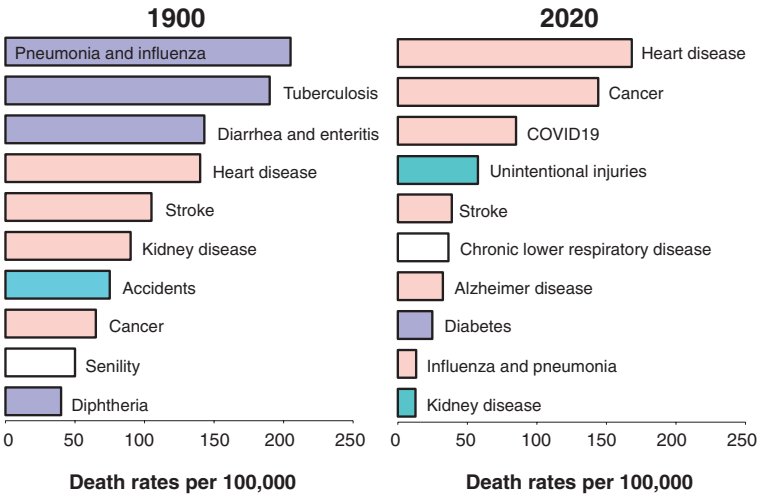

Fig. 1.2 Ten leading causes of death in the United States, 1900 and 2020. Although the definitions of the diseases in this figure are not exactly compare 1900 with 2020, the bars in the graphs are color coded to show chronic diseases *(pink)*, infectious diseases *(purple)*, injuries *(aqua)*, and diseases of aging *(white)*. (Data for 1900 are redrawn from Grove RD, Hetzel AM. *Vital Statistics Rates of the United States, 1940–1960*. Washington, DC: US Government Printing Office; 1968; and Kochanek KD, Murphy SL, Xu JQ, Tejada-Vera B. Deaths: Final data for 2014. *Natl Vital Stat Rep*. 2016;65(4):1–122. [Hyattsville, MD: National Center for Health Statistics.]). Data for 2020 are from Murphy SL, Kochanek KD, Xu JQ, Arias E. *Mortality in the United States, 2020*. NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics; 2021. Available at: https://dx.doi.org/10.15620/cdc:112079.).

TABLE 1.1 **Ten Leading Causes of Death and Their Percentages of All Deaths, United States, 2020**

Rank	Cause of Death	Number of Deaths	Percent of Total Deaths	Age-Adjusted Death Rate Per 100,000
	All Causes	33,83,729	100	
1	Heart disease	6,96,962	20.6%	168.2
2	Cancer	6,02,350	17.8%	144.1
3	COVID-19	3,50,831	10.4%	85
4	Accidents (unintentional injuries)	2,00,955	5.9%	57.6
5	Stroke (cerebrovascular diseases)	1,60,264	4.7%	38.8
6	Chronic lower respiratory diseases	1,52,657	4.5%	36.4
7	Alzheimer's disease	1,34,242	4.0%	32.4
8	Diabetes	1,02,188	3.0%	24.8
9	Influenza and pneuomnia	53,544	1.6%	13
10	Kidney disease	52,547	1.6%	12.7

Murphy SL, Kochanek KD, Xu JQ, Arias E. *Mortality in the United States, 2020.* NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics; 2021. Available at: https://dx.doi.org/10.15620/cdc:112079. Accessed May 08, 2023.

the COVID-19 pandemic have emerged and the incidence of tuberculosis has increased, infectious diseases are once again becoming major public health problems. Table 1.1 shows the 10 leading causes of death in the United States in 2014. The three leading causes—heart disease, cancer, and COVID-19—account for almost 55% of all deaths, an observation that suggests specific targets for prevention if a significant reduction in mortality is to be achieved.

Another demonstration of changes that have taken place over time is seen in Fig. 1.3, which shows the life expectancy at birth by sex between 2002 and 2020 (panel A) and by Hispanic origin and race in 2019 and 2020 (panel B) in the United States.

While the life expectancy has dramatically increased in both sexes over 20 years, most of these public health gains have been swept by the COVID-19 pandemic deaths as we can see from the sharp decline in life expectancy in both sexes and all races.

EPIDEMIOLOGY AND PREVENTION

A major use of epidemiologic evidence is to identify subgroups in the population who are at high risk for disease. Why should we identify such high-risk groups? First, if we can identify these high-risk groups, we can direct preventive efforts, such as screening programs for early disease detection, to populations who may not have been screened before and are most likely to benefit from any interventions that are developed for the disease. In sub-Saharan Africa, targeted HIV counseling and testing to men and women who are not aware of their status can effectively reduce epidemics if they are linked to care, started on antiretroviral therapy, and continued in care such that their viral load is undetectable.

Second, if we can identify such groups, we may be able to identify the specific factors or characteristics that put them at high risk and then try to modify those factors. It is important to keep in mind that such risk factors may be of two types. Characteristics such as age, sex, and race, for example, are not modifiable, although they may permit us to identify high-risk groups. On the other hand, characteristics such as obesity, smoking, diet, sexual practices, and other lifestyle factors may be potentially modifiable and may thus provide an opportunity to develop and introduce new prevention programs aimed at reducing or changing specific exposures or risk factors.

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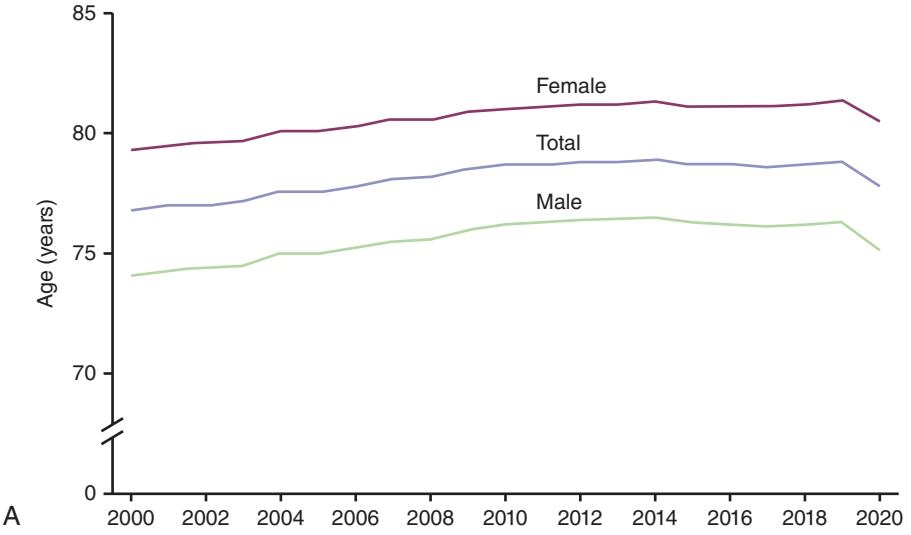
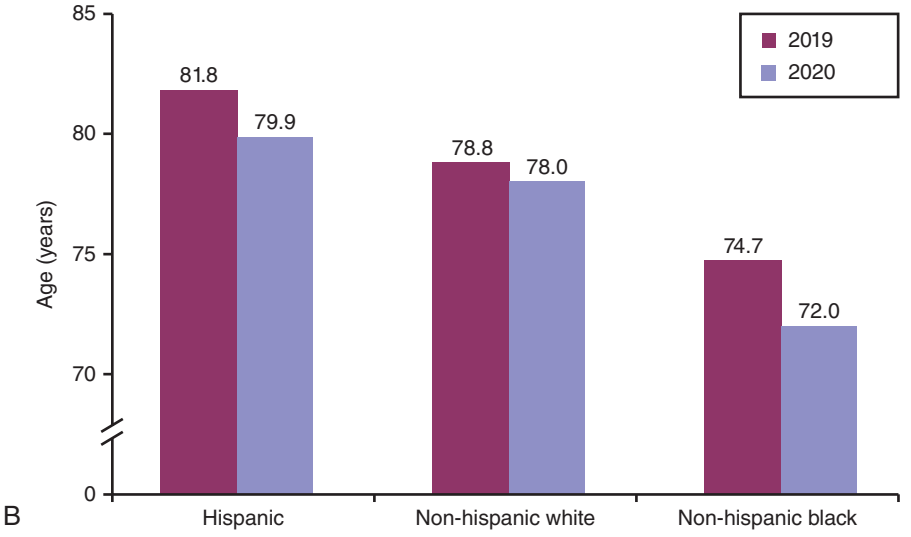


Notes: Life expectancies for 2019 by hispanic origin and race are not final estimates; see technical notes. Estimates are based on provisional data from January 2020 through June 2020.
Source: National center for health statistics, National vital statistics system, Mortality data.



Notes: Life expectancies for 2019 by hispanic origin and race are not final estimates; see technical notes. Estimates are based on provisional data from January 2020 through June 2020.
Source: National center for health statistics, National vital statistics system, Mortality data.

Fig. 1.3 **(A)** Life expectancy at birth by sex: United States, 2000–2020. **(B)** Life expectancy at birth by Hispanic origin and race: United States, 2019 and 2020. (From Arias E, Ejada-Vera B, Ahmad F. Provisional life expectancy estimates for January through June, 2020. Vital Statistics Rapid Release; no 10. Hyattsville, MD: National Center for Health Statistics. February 2021.)

Primary, Secondary, and Tertiary Prevention

In discussing prevention, it is helpful to distinguish among primary, secondary, and tertiary prevention (Table 1.2).

Primary prevention denotes an action taken to prevent the development of a disease in a person who is well and does not (yet) have the disease in question. For example, we can immunize a person against certain diseases so that the disease never develops or, if a disease is environmentally induced, we can prevent a person's exposure to the environmental factor involved and thereby prevent the development of the disease. Primary prevention is our goal. For example, we know that most lung cancers are preventable. If we can help to stop people from ever smoking, we can eliminate 80% to 90% of lung and other cancers in human beings. However, although our aim is to prevent diseases from occurring in human populations, for many diseases, such as prostate cancer and Alzheimer disease, we do not yet have the biologic, clinical, or epidemiologic knowledge on which to base effective primary prevention programs.

While the term *primordial prevention* precedes primary prevention, it is not commonly used. *Primordial prevention* denotes the prevention of the exposure to the risk factor of the disease of interest. For example, primordial prevention of hypertension should start in childhood through physical activity, low-sodium diet, no consumption of sugar-sweetened beverages, etc.[5]

Secondary prevention involves identifying people in whom a disease process has already begun, but who have not yet developed clinical signs and symptoms of the illness. This period in the natural history of a disease is called the *preclinical phase* of the illness and is discussed in depth in Chapter 18. Once a person develops clinical signs or symptoms, it is generally assumed that under ideal conditions the person will seek and obtain prompt medical advice. Our objective with secondary prevention is to detect the disease earlier than it would have been detected with usual care. By detecting the disease at an early stage in its natural history, often through screening, it is hoped that treatment will be easier and/or more effective. For example, most cases of early stage breast cancer in older women can be detected through mammography. Several recent studies indicate that routine testing of the stool for occult blood can detect treatable colon cancer early in its natural history, but colonoscopy is a better test, although far more expensive and invasive. The rationale for secondary prevention is that if we can identify disease earlier in its natural history than would ordinarily occur, intervention measures may be more effective and life prolonged. Perhaps we can prevent mortality or complications of the disease and use less invasive or less costly treatment to do so in individuals whose disease is diagnosed at an earlier stage. Evaluating screening for disease and the place of such intervention in the framework of disease prevention are discussed in Chapter 18.

Tertiary prevention denotes preventing complications in those who have already developed signs and symptoms of an illness and have been diagnosed (i.e., people who are in the clinical phase of their illness). This is generally achieved through prompt and appropriate treatment of the illness combined with ancillary approaches, such as physical therapy, that are designed to prevent complications such as joint contractures.

TABLE 1.2 Three Types of Prevention

Type of Prevention	Definition	Examples
Primary	Preventing the *initial development* of a disease	Immunization, reducing exposure to a risk factor
Secondary	Early detection of *existing disease* to reduce severity and complications	Screening for cancer
Tertiary	Reducing the *impact of the disease*	Rehabilitation for stroke

Two Approaches to Prevention: A Different View

Two possible approaches to prevention are a population-based approach and a high-risk approach.[6] In the population-based approach, a preventive measure is widely applied to an entire population. For example, prudent dietary advice for preventing coronary disease or advice against smoking may be provided to an entire population using mass media and other health education approaches. An alternate approach is to target a high-risk group with the preventive measure. Thus, screening for cholesterol in children might be restricted to children from high-risk families. Clearly, a measure

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applied to an entire population must be relatively inexpensive and noninvasive or it cannot be thought as cost-effective. A measure that is to be applied to a high-risk subgroup of the population may be more expensive and may be more invasive or inconvenient, but also must be able to correctly identify individuals with the disease. More on screening tests is discussed in Chapter 18. Population-based approaches can be considered public health approaches, whereas high-risk approaches more often require a clinical action to identify the high-risk group to be targeted. In most situations, a combination of both approaches is ideal. Often a high-risk approach, such as prevention counseling, is limited to brief encounters with physicians. These approaches are discussed further in Chapter 19.



"You've got whatever it is that's going around."

Fig. 1.4 "You've got whatever it is that's going around." (Al Ross/The New Yorker Collection/The Cartoon Bank.)

EPIDEMIOLOGY AND CLINICAL PRACTICE

Epidemiology is critical not only to public health but also to clinical practice. The practice of medicine is dependent on population data. For example, if a physician hears an apical systolic murmur, a heart sound produced when blood flows across the heart valves, how does he or she know whether it represents mitral regurgitation? Where did this knowledge originate? The diagnosis is based on correlation of the clinical findings (such as the auscultatory findings—sounds heard using a stethoscope) with the findings of surgical pathology or autopsy and with the results of echocardiography, magnetic resonance, or catheterization studies in a large group of patients. Thus, the process of diagnosis is population based (see Chapter 5). The same holds for prognosis. For example, a patient asks his physician, "How long do I have to live, doctor?" and the doctor replies, "Six months to a year." On what basis does the physician prognosticate? They do so based on experience with large groups of patients who have had the same disease, were observed at the same stage of disease, and received the same treatment. Again, prognostication is based on population data (see Chapter 6). Finally, selection of appropriate therapy is also population based. Randomized clinical trials that study the effects of a treatment in large groups of patients are the ideal means (the so-called gold standard) for identifying appropriate therapy (see Chapters 10 and 11). Thus population-based concepts and data underlie the critical processes of clinical practice, including diagnosis, prognostication, and selection of therapy. In effect, the physician applies a population-based probability model to the patient on the examining table.

Fig. 1.4 shows a physician demonstrating that the practice of clinical medicine relies heavily on population concepts. What is portrayed humorously here is a true commentary on one aspect of pediatric practice—a pediatrician often makes a diagnosis based on what the parent tells them over the telephone and on what they know about which illnesses, such as viral and bacterial infections, are "going around" in the community. Thus, the data available about illness in the community can be very helpful in suggesting a diagnosis, even if they are not conclusive. Data regarding the etiology of sore throats according to a child's age are particularly relevant (Fig. 1.5). If the infection occurs very early in life, it is likely to be viral in origin. If it occurs at ages 4 to 7 years, it is likely to be streptococcal in origin. In an older child, *Mycoplasma* becomes more typical. Although these data do not make the diagnosis, they do provide the physician or other health care provider with a good clue as to what agent or agents to suspect.

EPIDEMIOLOGIC APPROACH

How does the epidemiologist proceed to identify the cause of a disease? Epidemiologic reasoning is a multistep process. The first step is to determine whether a statistical association exists between exposure to a factor (e.g., an environmental agent) or a characteristic of a

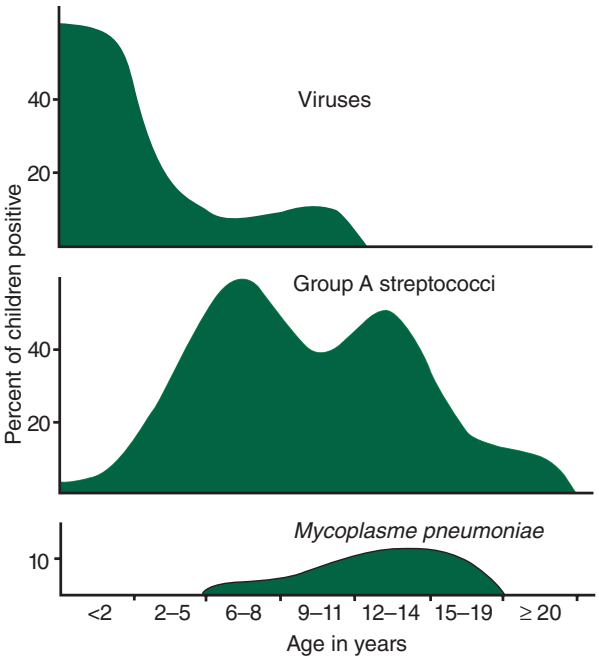

Fig. 1.5 Frequency of agents by age of children with pharyngitis, 1964–1965. (From Denny FW. The replete pediatrician and the etiology of lower respiratory tract infections. *Pediatr Res.* 1969;3:464–470.)

person (e.g., an increased serum cholesterol level) and the presence of the disease in question. We do this by studying the characteristics of groups and the characteristics of individuals.

If we find there is indeed an association between an exposure and a disease, is it necessarily a causal relationship? No, not all associations are causal. The second step therefore is to try to derive appropriate inferences about a possible causal relationship from the patterns of the associations that have been previously found. These steps are discussed in detail Chapter 14.

Epidemiology often begins with descriptive data. For example, Fig. 1.6 shows rates of gonorrhea in the United States and its territories in 2011 and 2020 by state. Clearly, there are marked regional variations in reported cases of gonorrhea. The first question to ask when we see such differences between two groups or two regions or at two different times is, "Are these differences real?" In other words, are the data from each area of comparable quality? Before we try to interpret the data, we should be satisfied that the data are valid. If the differences are real, then we ask, "Why have these differences occurred?" Are there differences in potential exposures between high-risk and low-risk areas, or are there differences in the people who live in those areas? This is where what has been named analytic epidemiology begins its investigation.

Many years ago, it was observed that communities in which the natural level of fluoride in the drinking water varied were related to the frequency of dental caries in the permanent teeth of residents. Communities that had low natural fluoride levels had high levels of caries, and communities that had higher levels of fluoride in their drinking water had low levels of caries (Fig. 1.7). This finding suggested that fluoride might be an effective prevention intervention if it were artificially added to the drinking water supply. A trial was therefore carried out to test the hypothesis. Although, ideally, we would like to randomize a group of people either to receive fluoride or to receive no fluoride, this was not possible to do with drinking water because each community generally shares a common water supply. Consequently, two similar communities in upstate New York, Kingston and Newburgh, were chosen for the trial. The DMF index, a count of decayed, missing, and filled teeth, was used. Baseline data were collected in both cities, and at the start of the study, the DMF indices were comparable in each age group in the two communities. The water in Newburgh was then fluoridated, and the children were reexamined a decade later. Fig. 1.8 shows that, in each age group, the DMF index in Newburgh had dropped significantly 10 years or so later, whereas in Kingston, there was no change. This is strongly suggestive evidence that fluoride was preventing caries.

It was possible to go one step further in trying to demonstrate a causal relationship between fluoride ingestion and low rates of caries. The issue of fluoridating water supplies has been extremely controversial, and in certain communities in which water has been fluoridated, there have been referenda to stop the fluoridation. It was therefore possible to look at the DMF index in communities such as Antigo, Wisconsin, in which fluoride had been added to its water supply and then, after a referendum, fluoridation had been stopped. As seen in Fig. 1.9, after the fluoride was removed, the DMF index rose. This provided yet a further piece of evidence that fluoride acted to prevent dental caries.

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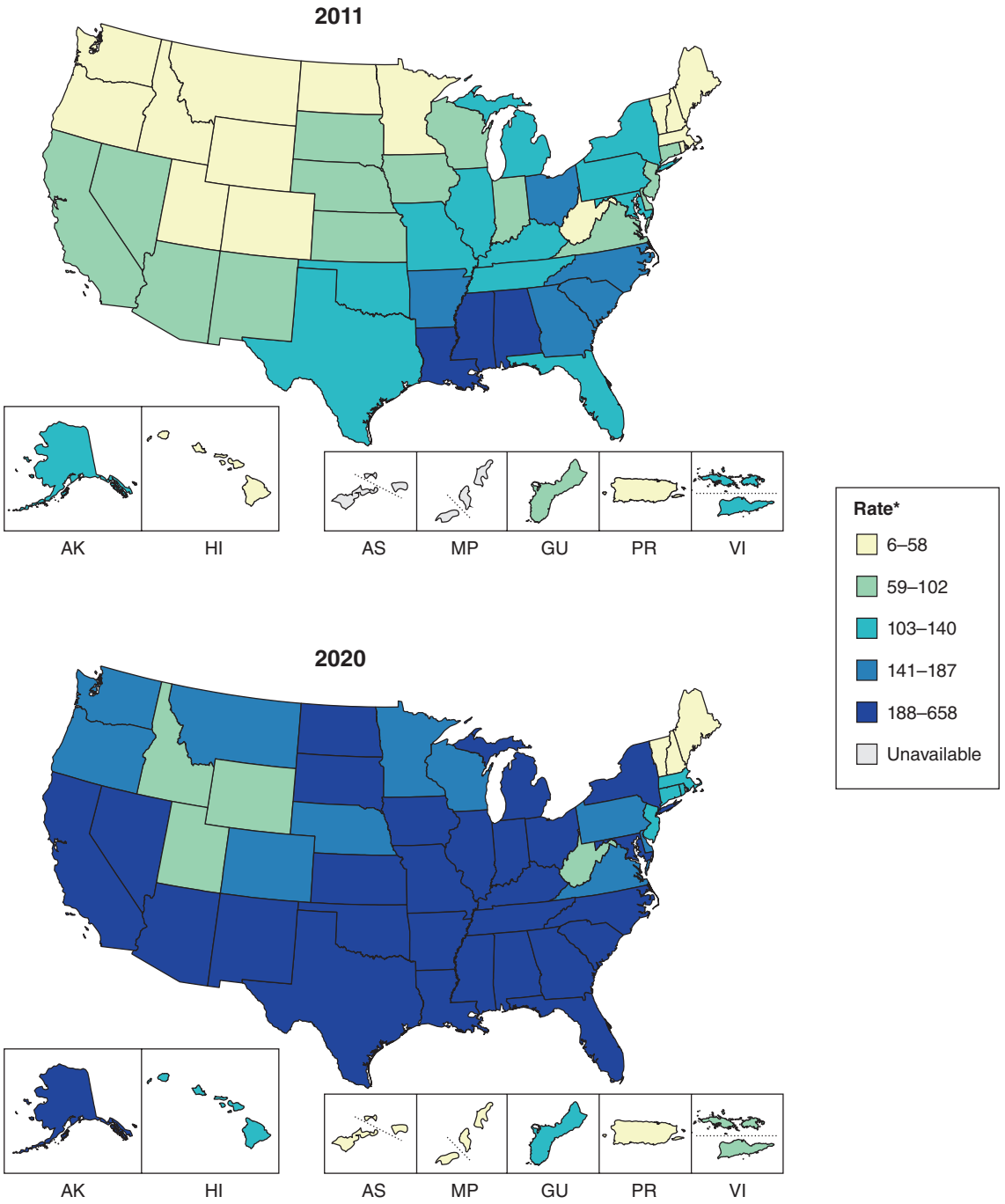

Fig. 1.6 Gonorrhea—rates of reported cases by state, United States and Territories, 2011 and 2020. In 2011, eight states and the District of Columbia (DC; 16.1% of available areas) had a rate of reported gonorrhea greater than or equal to 141 cases per 100,000 population. This increased to 38 states and DC (69.6% of available areas) in 2020. (From Centers for Disease Control and Prevention. National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Division of STD Prevention. Sexually Transmitted Disease Surveillance 2020. https://www.cdc.gov/std/statistics/2020/figures/2020-STD-Surveillance-Gonorrhea.pptx)

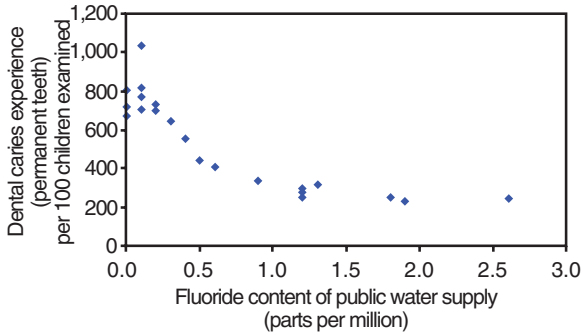

Fig. 1.7 Relationship between rate of dental caries in children's permanent teeth and fluoride content of public water supply. (Modified from Dean HT, Arnold Jr FA, Elvove E. Domestic water and dental caries: V. Additional studies of the relation of fluoride in domestic waters to dental caries experience in 4,425 white children aged 12 to 14 years of 13 cities in 4 states. *Public Health Rep.* 1942;57:1155–1179.)

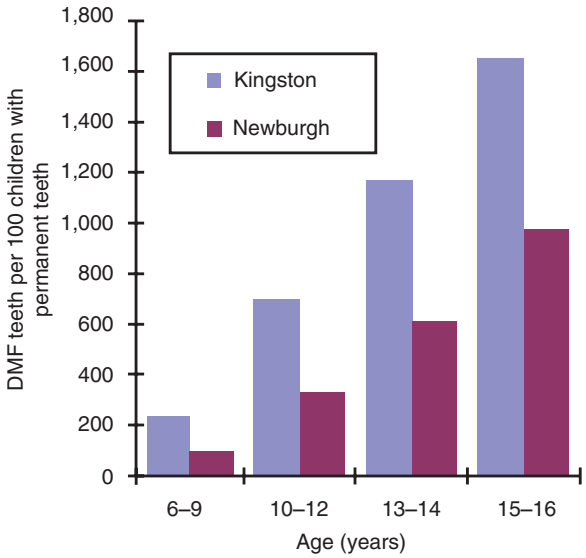

Fig. 1.8 Decayed, missing, and filled teeth *(DMF)* indices after 10 years of fluoridation, 1954–1955. (Modified from Ast DB, Schlesinger ER. The conclusion of a 10-year study of water fluoridation. *Am J Public Health.* 1956;46:265–271. Copyright 1956 by the American Public Health Association. Modified with permission.)

FROM OBSERVATIONS TO PREVENTIVE ACTIONS

In this section, three examples from history are discussed that demonstrate how epidemiologic observations have led to effective preventive measures in human populations.

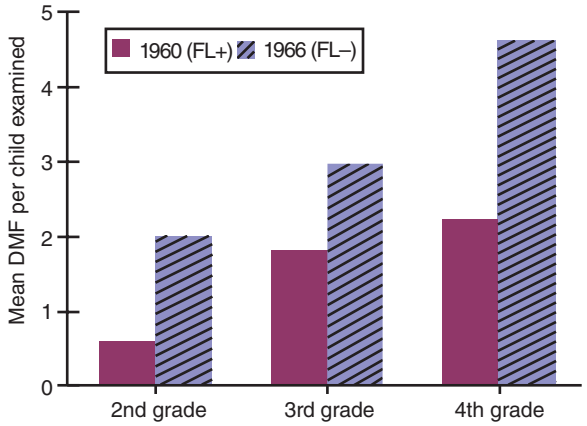

Fig. 1.9 Effect of discontinuing fluoridation in Antigo, Wisconsin, November 1960. *DMF,* Decayed, missing, and filled teeth; *FL+*, during fluoridation; *FL−*, after fluoridation was discontinued. (Modified from Lemke CW, Doherty JM, Arra MC. Controlled fluoridation: the dental effects of discontinuation in Antigo, Wisconsin. *J Am Dent Assoc.* 1970;80:782–786. Reprinted by permission of ADA Publishing Co., Inc.)

Ignáz Semmelweis and Childbed Fever

Ignáz Semmelweis (Fig. 1.10) was born in 1818 and began as a student of law until he left his studies to pursue medical training. He specialized in obstetrics and became interested in a major clinical and public health problem of the day: childbed fever, also known as puerperal fever (the word "puerperal" means related to childbirth or to the period after the birth).

In the early 19th century, childbed fever was a major cause of death among women shortly after childbirth, with mortality rates from childbed fever as high as 25%. Many theories of the cause of childbed fever were popular at the time, including atmospheric toxins, "epidemic constitutions" of some women, putrid air, or solar and magnetic influences. This period was a time of growing interest in pathologic anatomy. Because the cause of childbed fever remained a mystery, great interest arose in associating the findings at autopsies of women who had died of the disease with the clinical manifestations that characterized them while ill after childbirth.

Semmelweis was placed in charge of the First Obstetrical Clinic of the Allgemeine Krankenhaus (General Hospital) in Vienna in July 1846. At that time there were two obstetrical clinics, the First and the Second. Pregnant women were admitted for childbirth to the First

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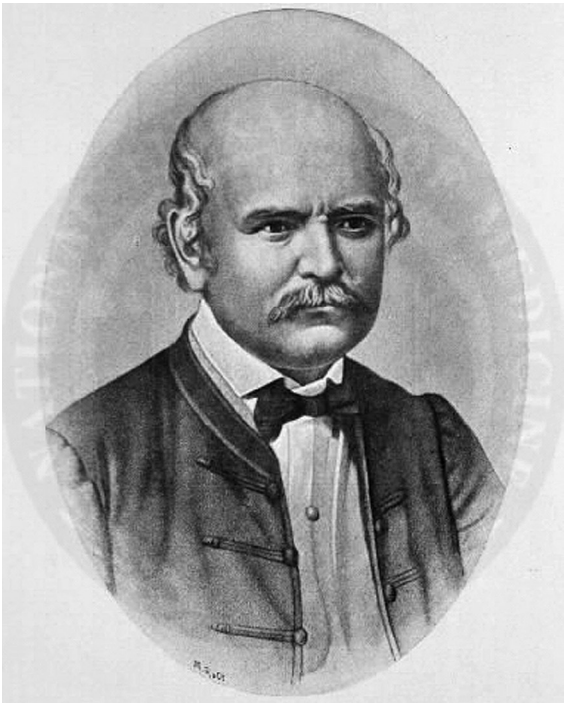

Fig. 1.10 Portrait of Ignáz Philipp Semmelweis. (From The National Library of Medicine.)

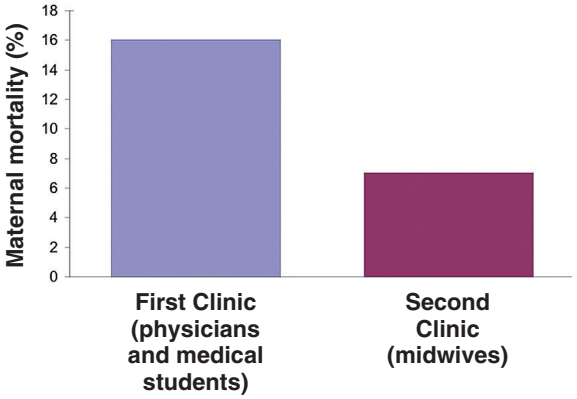

Fig. 1.11 Maternal mortality due to childbed fever, First and Second Clinics, General Hospital, Vienna, Austria, 1842. (Modified from the Centers for Disease Control and Prevention: Hand hygiene in health care settings—supplemental. www.cdc.gov/handhygiene/download/hand_hygiene_supplement.ppt. Accessed April 11, 2013.)

Clinic or to the Second Clinic on an alternating 24-hour basis. The First Clinic was staffed by physicians and medical students and the Second Clinic by midwives. Physicians and medical students began their days performing autopsies on women who had died from childbed fever; they then proceeded to provide clinical care for women hospitalized in the First Clinic for childbirth. The midwives staffing the Second Clinic did not perform autopsies. Semmelweis had been impressed by mortality rates in the two clinics in 1842 (Fig. 1.11). Mortality in the First Clinic was more than twice as high as in the Second Clinic—16% compared with 7%.

Semmelweis surmised that mortality was higher in the First Clinic than in the Second because the physicians and medical students went directly from the autopsies to their patients. Many of the women in labor had multiple examinations by physicians and by medical students learning obstetrics. Often these manual examinations traumatized the tissues of the vagina and uterus. Semmelweis suggested that the hands of physicians and medical students were transmitting disease-causing particles from the cadavers to the women who were about to deliver. His suspicions were confirmed in 1847 when his friend and colleague Jakob Kolletschka died from an infection contracted when he was accidentally punctured with a medical student's knife while performing an autopsy. The autopsy on Kolletschka showed pathology very similar to that of the women who were dying from childbed fever. Semmelweis concluded that physicians and medical students were carrying the infection from the autopsy room to the patients in the First Clinic and that this accounted for the high mortality rates from childbed fever in the First Clinic. Mortality rates in the Second Clinic remained low because the midwives who staffed the Second Clinic had no contact with the autopsy room.

Semmelweis then developed and implemented a policy for the physicians and medical students in the First Clinic, a policy designed to prevent childbed fever. He required the physicians and medical students in the First Clinic to wash their hands and to brush under their fingernails after they had finished the autopsies and before they encountered any of the patients. As seen in Fig. 1.12, in 1848, mortality in the First Clinic dropped from 12.2% to 2.4%, a rate comparable to that seen in the Second Clinic for the same year. When Semmelweis was later replaced by an obstetrician who did not subscribe to Semmelweis's theories, and who therefore eliminated the policy of required handwashing, mortality rates from childbed fever rose again in the First Clinic—further evidence supporting a causal relationship.

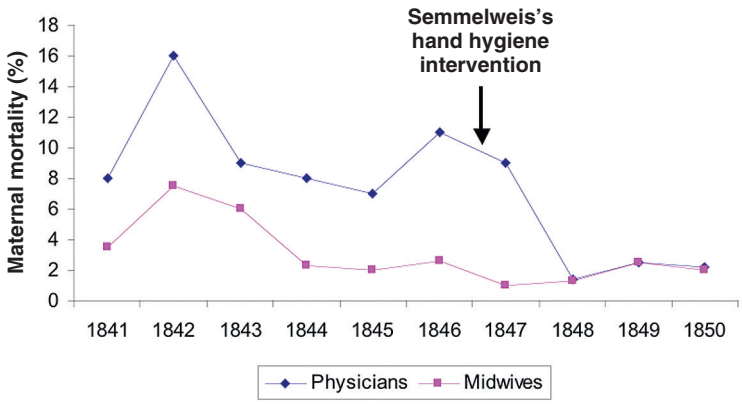

Fig. 1.12 Maternal mortality due to childbed fever, by type of care provider, General Hospital, Vienna, Austria, 1841–1850. (Modified from Mayhall GC. *Hospital Epidemiology and Infection Control.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.)

Unfortunately, for many years Semmelweis refused to present his findings at major meetings or to submit written reports of his studies to medical journals. His failure to provide supporting scientific evidence was at least partially responsible for the failure of the medical community to accept his hypothesis of causation of childbed fever and his further proposed intervention of handwashing before examining each patient. Among other factors that fostered resistance to his proposal was the reluctance of physicians to accept the conclusion that by transmitting the agent responsible for childbed fever, they had been inadvertently responsible for the deaths of large numbers of women. In addition, physicians claimed that washing their hands before seeing each patient would be too time consuming. Another major factor is that Semmelweis was, to say the least, undiplomatic and had alienated many senior figures in medicine. Because of all of these factors, many years passed before a policy of handwashing was broadly adopted. An excellent biography of Semmelweis by Sherwin Nuland was published in 2003.[7]

The lessons of this story for successful policy making are still relevant today to the challenge of enhancing both public and professional acceptance of evidence-based prevention policies. These lessons include the need for clearly presenting supporting scientific evidence for a proposed intervention, the need for implementation of the proposed intervention to be perceived as feasible and cost-effective, and the need to lay the necessary groundwork for the policy, including garnering professional as well as community and political support.

Years later, the major cause of childbed fever was recognized to be a streptococcal infection. Semmelweis's major findings and recommendations ultimately had worldwide effects on the practice of medicine. Amazingly, his observations and suggested interventions preceded any knowledge of germ theory and thus proved that it is possible to implement a prevention strategy even when the exact cause of the disease is not known. However, it is also of interest that, although the need for handwashing has now been universally accepted, recent studies have reported that many physicians in hospitals in the United States and in other developed countries still fail to wash their hands as prescribed (Table 1.3).

TABLE 1.3 Compliance With Hand Hygiene Among Physicians, by Specialty, at University of Geneva Hospitals

Physician Specialty	No. of Physicians	Compliance With Hand Hygiene (% of Observations)
Internal medicine	32	87.3
Surgery	25	36.4
Intensive care unit	22	62.6
Pediatrics	21	82.6
Geriatrics	10	71.2
Anesthesiology	15	23.3
Emergency medicine	16	50.0
Other	22	57.2

Data from Pittet D. Hand hygiene among physicians: performance, beliefs, and perceptions. *Ann Intern Med.* 2004;141:1–8.

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Fig. 1.13 Portrait of Edward Jenner. (From the Wellcome Historical Medical Museum and Library, London.)

Edward Jenner and Smallpox

Edward Jenner (Fig. 1.13) was born in 1749 and became very interested in the problem of smallpox, which was a worldwide scourge. In the late 18th century, 400,000 people died from smallpox each year and one-third of survivors were blinded as a result of corneal infections. It was known that those who survived smallpox were subsequently immune to the disease, and consequently it became a common preventive practice to infect healthy individuals with smallpox by administering to them material taken from smallpox patients, a procedure called *variolation*. However, this was not the optimal method: some variolated individuals died from the resulting smallpox, infected others with smallpox, or developed other infections.

Jenner was interested in finding a better, safer approach to preventing smallpox. He observed, as had other people before him, that dairy maids, the young women whose occupation was milking cows, developed a mild disease called cowpox. Later, during smallpox outbreaks, smallpox appeared not to develop in these young women. In 1768 Jenner heard a claim from a dairy maid, "I can't take the smallpox for I have already had the cowpox." These data were observations and were not based on any rigorous study, but Jenner became convinced that cowpox could protect against smallpox and decided to test his hypothesis.



Fig. 1.14 *Une des premières vaccinations d'Edward Jenner* ("One of the first vaccinations by Edward Jenner"), by Gaston Melingue. (Reproduced by permission of the Bibliothèque de l'Académie Nationale de Médecine, Paris, 2007.)

Fig. 1.14 shows a painting by Gaston Melingue of Edward Jenner performing the first vaccination in 1796. (The term "vaccination" is derived from *vacca*, the Latin word for "cow.") In this painting, a dairy maid, Sarah Nelmes, is bandaging her hand after just having had some cowpox material removed. The cowpox material is being administered by Jenner to an 8-year-old "volunteer," James Phipps. Jenner was so convinced that cowpox would be protective that 6 weeks later, to test his conviction, he inoculated the child with material that had just been taken from a smallpox pustule. The child did not contract the disease. We shall not deal in this chapter with the ethical issues and implications of this experiment. (Clearly, Jenner did not have to justify his study before an institutional review board!) In any event, the results of the first vaccination and of what followed eventually saved literally millions of human beings throughout the world from disability and death caused by the scourge of smallpox. The important point is that Jenner knew nothing about viruses and nothing about the biology of the disease. He operated purely on observational data that provided him with the basis for a preventive intervention.

In 1967 the World Health Organization (WHO) began international efforts to eradicate smallpox using

vaccinations with vaccinia virus (cowpox). It has been estimated that, until that time, smallpox afflicted 15 million people annually throughout the world, of whom 2 million died and millions of others were left blind or disfigured. In 1980 the WHO certified that smallpox had been eradicated. The smallpox eradication program,[8] directed at the time by Dr. D.A. Henderson (Fig. 1.15), is one of the greatest disease prevention achievements in human history. The WHO estimated that 350 million new cases had been prevented over a 20-year period. However, after the terrorist attacks that killed nearly 3,000 people in the World Trade Center in New York City on September 11, 2001, worldwide concern developed about potential bioterrorism in the wake of the 2001 anthrax attacks. Ironically, the possibility that smallpox virus might be used for such a purpose reopened issues regarding smallpox and vaccination that many thought had been permanently relegated to history by the successful efforts at eradication of the disease. The magnitude of the smallpox bioterrorism threat, together with issues of vaccinia risk—both to those vaccinated and to those coming in contact with vaccinees, especially in hospital environments—are among many that have had to be addressed. (It should, however, be noted that the cost-benefit of smallpox vaccination strongly favors benefit.[9]) However, often only limited or equivocal data are available on these issues to guide the development of relevant public health prevention policy relating to a potential bioterrorism threat of using smallpox as a weapon.

John Snow and Cholera

Another example of the translation of epidemiologic observations into public policy immortalized John Snow, whose portrait is seen in Fig. 1.16. Snow lived in the 19th century and was well known as the anesthesiologist who administered chloroform to Queen Victoria during childbirth. Snow's true love, however, was the epidemiology of cholera, a disease that was a major problem in England in the middle of the 19th century. In the first week of September 1854, approximately 600 people living within a few blocks of the Broad Street pump in London died of cholera. At that time, the Registrar General was William Farr. Snow and Farr



Fig. 1.15 Photograph of Dr. D.A. Henderson (1928–2016), who directed the World Health Organization Smallpox Eradication Program.

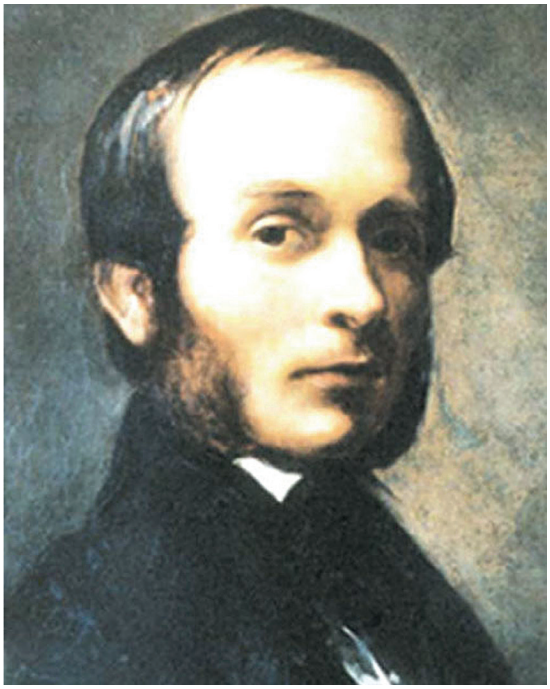

Fig. 1.16 Portrait of John Snow. (Portrait in oil by Thomas Jones Barker, 1847, in Zuck D. Snow, Empson and the Barkers of Bath. *Anaesthesia.* 2001;56:227–230.)

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had a major disagreement about the cause of cholera. Farr adhered to what was called the *miasmatic* theory of disease. According to this theory, which was commonly held at the time, disease was transmitted by a *miasm*, or cloud, that clung low on the surface of the earth. If this were so, we would expect that people who lived at lower altitudes would be at greater risk of contracting a disease transmitted by this cloud than those living at higher elevations.

Farr collected data to support his hypothesis (Table 1.4). The data are quite consistent with his hypothesis: the lower the elevation, the higher the mortality rate from cholera. Snow did not agree; he believed that cholera was transmitted through contaminated water (Fig. 1.17). In London at that time, water was obtained by signing up with one of the water supply companies. The intakes for the water companies were in a very polluted part of the Thames River. At one point in time, one of the companies, the Lambeth Company, for technical, non–health-related reasons, shifted its water intake upstream in the Thames to a less polluted part of the river; the other companies did not move the locations of their water intakes. Snow reasoned therefore that based on his hypothesis that contaminated water caused cholera, the mortality rate from cholera would be lower in people getting their water from the Lambeth Company than in those obtaining their water from the other companies. He carried out what we

TABLE 1.4 Deaths From Cholera in 10,000 Inhabitants by Elevation of Residence Above Sea Level, London, 1848–1849

Elevation Above Sea Level (ft)	No. of Deaths
<20	102
20–40	65
40–60	34
60–80	27
80–100	22
100–120	17
340–360	8

Data from Farr W. *Vital Statistics: A Memorial Volume of Selections from the Reports and Writings of William Farr* (edited for the Sanitary Institute of Great Britain by Noel A. Humphreys). London: The Sanitary Institute; 1885.



A DROP OF LONDON WATER.

Fig. 1.17 A drop of Thames water, as depicted by *Punch* in 1850. (From The wonders of a London water drop. *Punch Magazine.* May 11, 1850;461:188.)

currently call "shoe-leather epidemiology"—going from house to house, counting all deaths from cholera in each house, and determining which company supplied water to each house.

Snow's findings are shown in Table 1.5. The table shows the number of houses, the number of deaths from cholera, and the deaths per 10,000 houses. Although this is not an ideal way to calculate a rate, because a house can contain different numbers of people, it is not a bad approximation. We see that in houses served by the Southwark and Vauxhall Company, which obtained its water from a polluted part of the Thames, the death rate was 315 deaths per 10,000 houses. In homes supplied by the Lambeth Company, which had relocated its water intake upstream, the rate was only 38 deaths per 10,000 houses. His data were so convincing that they led Farr, the Registrar General, to require the registrar of each district in south London to record which water company supplied each house in which a person died of cholera. Remember that, in Snow's day, the enterotoxin *Vibrio cholerae* was unknown. Nothing was known about the biology of the disease. Snow's conclusion that contaminated water was associated with cholera was based entirely on observational data.[10]

The point is that, although it is extremely important for us to maximize our knowledge of the biology and pathogenesis of disease, it is not always necessary to know every detail of the possible pathogenic mechanisms to prevent disease. For example, we know that virtually every case of rheumatic fever and rheumatic heart disease occurred after a streptococcal infection. Though *Streptococcus* has been studied and analyzed extensively, we still do not know how and why it causes rheumatic fever. We do know that after a severe streptococcal infection, as seen in military recruits, rheumatic fever does not develop in 97 of every 100 infected persons. In civilian populations, such as schoolchildren, in whom the infection is less severe, rheumatic fever develops in only 3 of every 1,000 infected schoolchildren but not in the remaining 997.[11] Why does the disease not develop in those 97 recruits and 997 schoolchildren if they are exposed to the same organism? We do not know. Is the illness the result of an undetected difference in the organism, or is it caused by a cofactor that may facilitate the adherence of streptococci to epithelial cells? What we do know is that, even without fully understanding the chain of pathogenesis from infection with *Streptococcus* to rheumatic fever, we can prevent virtually every case of rheumatic fever if we either prevent or promptly and adequately treat streptococcal infections, as has been the case in the United States. The absence of biologic knowledge about pathogenesis should not be a hindrance or an excuse for not implementing effective preventive services.

Fig. 1.18 shows mortality data for breast cancer and lung cancer in women in the United States. Breast

TABLE 1.5 Deaths From Cholera per 10,000 Houses, by Source of Water Supply, London, 1854

Water Supply	No. of Houses	Deaths from Cholera	Deaths per 10,000 Houses
Southwark and Vauxhall Co.	40,046	1,263	315
Lambeth Co.	26,107	98	38
Other districts in London	256,423	1,422	56

Data modified from Snow J. On the mode of communication of cholera. In: *Snow on Cholera: A Reprint of Two Papers by John Snow, M.D.* New York: The Commonwealth Fund; 1936.

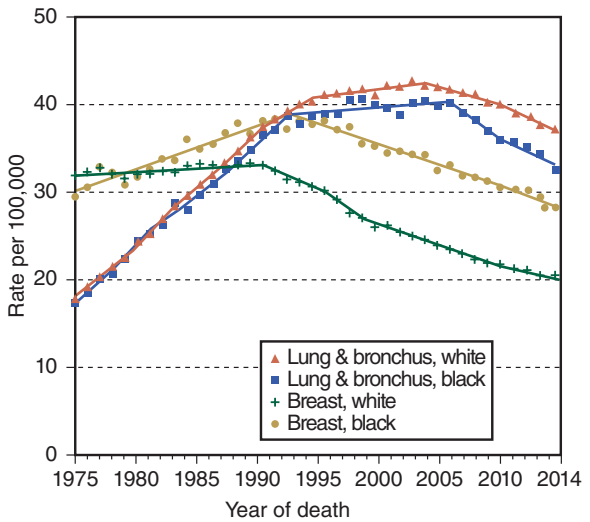

Fig. 1.18 Breast versus lung cancer mortality: White females versus Black females, United States, 1975–2014, age-adjusted to 2000 standard. (From Howlader N, Noone AM, Krapcho M, et al, eds. *SEER Cancer Statistics Review, 1975–2014, National Cancer Institute*. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website, April 2017. https://seer.cancer.gov/csr/1975_2014/browse_csr.php; *Figure 4.9*. Accessed April 14, 2017.)

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cancer mortality rates remained relatively constant over several decades, but showed evidence of decline in the early years of the 21st century. However, mortality from lung cancer in women has been increasing steadily, although it may have begun to stabilize, and even decrease slightly, in recent years. Since 1987, more women in the United States have died each year from lung cancer than from breast cancer. We are therefore faced with the tragic picture of a largely preventable form of cancer, lung cancer, which results from a personal habit, smoking, as the current leading cause of cancer death in American women.

In 1993, environmental tobacco smoke (secondhand smoke from other people's smoking) was classified as a known human carcinogen by the Environmental Protection Agency, which attributed about 3,000 lung cancer deaths in nonsmoking individuals each year to environmental tobacco smoke.

WHEN THE FREQUENCY OF A DISEASE DECLINES, WHO DESERVES THE CREDIT?

Over the past hundred or so years, mortality rates from several common infectious diseases have declined in the United States. For example, deaths from childhood infections such as diphtheria, pertussis (whooping cough), and scarlet fever (a streptococcal infection) have declined dramatically. In addition, US deaths from tuberculosis have dropped significantly.

It would be tempting to link these declines to improvements in vaccines or treatments that became available for these diseases during this time. However, in 1971 Edward Kass published the graphs shown in Fig. 1.19.[12] These graphs demonstrate that for each of these diseases, the major decline in mortality occurred many years before any effective vaccine or treatment became available. Fig. 1.20 shows a similar presentation

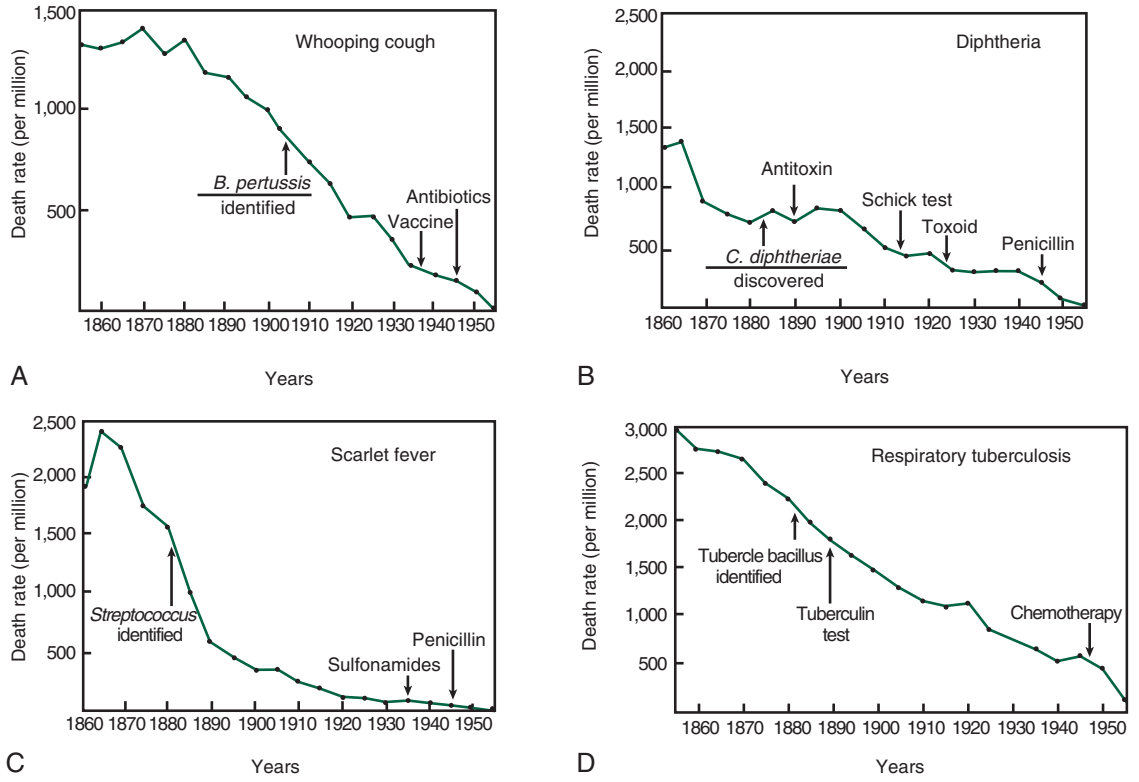

Fig. 1.19 Decline in death rates in England and Wales for **(A)** whooping cough, **(B)** diphtheria, **(C)** scarlet fever (children younger than 15 years of age), and **(D)** respiratory tuberculosis. (From Kass EH. Infectious diseases and social change. *J Infect Dis.* 1971;123:110–114.)

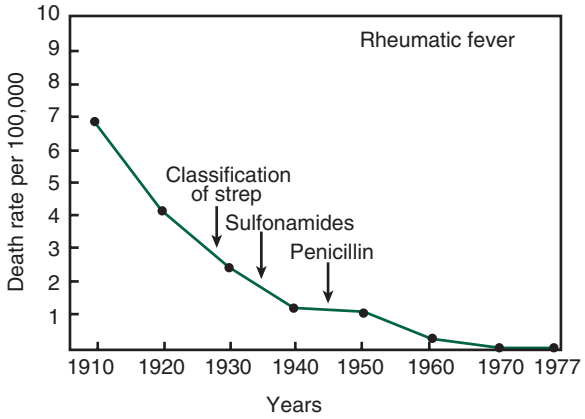

Fig. 1.20 Decline in crude death rates from rheumatic fever, United States, 1910–1977. (From Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T. Duckett Jones Memorial Lecture. *Circulation.* 1985;72:1155–1162.)

of mortality trends over time for rheumatic fever in the 20th century.[13] Clearly, most of the decline in rheumatic fever mortality occurred well before penicillin and other antistreptococcal treatments became available.

What can explain these dramatic declines even before any vaccine or treatment became available? Theoretically, it is possible that when we observe a decline in mortality from an infectious disease, human exposure to the organisms involved may have declined, or the virulence of the organism may have diminished. However, a more likely explanation for the decline in mortality in these and other examples is that they primarily result from improvements in social conditions: safer water and reduced exposures to pollutants unrelated to any medical intervention. In fact, Kass titled his 1971 paper, in which the graphs in Fig. 1.19 appeared, "Infectious Diseases and Social Change." Although the specific factors that were probably involved are not always clear, social determinants of health, including improved housing, sanitation and nutrition, in addition to simultaneous lifestyle changes, are major factors that are likely to have contributed significantly to the decline.

We are often eager to attribute temporal declines in mortality to medical interventions. However, the lesson illustrated by the examples presented here is that we should be cautious before we conclude that observed declines in mortality are a result of medical intervention. In view of difficulties in deriving inferences about the effectiveness of medical care solely from population-wide declines in mortality, rigorous epidemiologic studies are clearly essential to assess the effectiveness of different medical interventions. Some of the approaches used and the design of such studies for evaluating health services are discussed in Chapter 17.

INTEGRATING PREVENTION AND TREATMENT

Prevention and therapy all too often are viewed as mutually exclusive activities, as is shown in Fig. 1.21. However, prevention is integral to public health, but it is also integral to clinical practice. The physician's role is to maintain health, as well as to treat disease, but even treatment of disease includes a major component of prevention, which often involves other health care workers. Whenever we treat illness, we are preventing death, preventing complications in the patient, or preventing the impact on the patient's family. Thus, much



Fig. 1.21 Prevention and therapy viewed as mutually exclusive activities. (ZIGGY © 1986 ZIGGY AND FRIENDS, INC. Reprinted with permission of ANDREWS MCMEEL SYNDICATION. All rights reserved.)

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of the dichotomy between therapy and prevention is an illusion. Therapy involves secondary and tertiary prevention, the latter denoting the prevention of complications such as disability. At times it also involves primary prevention. Thus, the entire spectrum of prevention should be viewed as integral to both public health and clinical practice.

Two very different decisions in 2012 placed further emphasis on the link between prevention and treatment. In July 2012 the US Food and Drug Administration (FDA) approved the use of a drug, Truvada (combination tenofovir and emtricitabine [antiviral medications]; Gilead Sciences, Foster City, CA, United States), for preventing HIV infection in people who are at high risk of acquiring HIV infection (so-called preexposure prophylaxis [PrEP]). Since 2004 the drug had been marketed only for treatment of individuals already infected with HIV—both for those chronically infected and those exposed to a needle-stick or other traumatic risk (so-called postexposure prophylaxis [PEP]).

CONCLUSION

Epidemiology is an invaluable tool for providing a rational basis on which effective prevention programs can be planned and implemented. Epidemiology is valuable when conducting clinical investigations to evaluate both newly developed interventions for disease prevention as well as new therapies and those that have been in use for some time. The goal is to improve the control of disease through both prevention and treatment that will prevent deaths from the disease and will enhance the quality of life of those who have developed serious illness. The study designs used in epidemiology are discussed in later chapters.

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2

The Dynamics of Disease Transmission

I keep six honest serving-men
(They taught me all I knew);
Their names are What and Why and When
And How and Where and Who.
—Rudyard Kipling[1] (1865–1936)

LEARNING OBJECTIVES

- To introduce concepts related to disease transmission using the epidemiologic approach to communicable diseases as a model.
- To define important terms related to the occurrence of disease in a population.
- To calculate an attack rate and illustrate how it may be used to measure person-to-person transmission of a disease.
- To describe the steps in an outbreak investigation and introduce how cross-tabulation may be used to identify the source.

Human disease does not arise in a vacuum. It results from an interaction of the host (a person), the agent (e.g., a bacterium), and the environment (e.g., polluted air). Although some diseases are largely genetic in origin, virtually all disease results from an interaction of genetic, behavioral, and environmental factors, with the proportions differing for different diseases. Many of the underlying principles governing the transmission of disease are most clearly demonstrated using communicable diseases as a model. Hence this chapter primarily uses such diseases as examples in reviewing these principles. However, the concepts discussed are also applicable to diseases that are not infectious in origin (e.g., second-hand smoke causing cancer).

Disease has been classically described as the result of the epidemiologic triad shown in Fig. 2.1. According to this diagram, it is the product of an interaction of the human host, an infectious or other type of agent, and the environment that promotes the exposure. A vector, such as the mosquito or the deer tick, may be involved. For such an interaction to take place, the host must be susceptible. Human susceptibility is determined by a variety of factors including genetic background and behavioral, nutritional, and immunologic characteristics. The immune status of an individual is determined by many factors including prior experience both with natural infection and with immunization.

The factors that can cause human disease include biologic, physical, and chemical factors as well as other types, such as stress or behavioral risks, which may be harder to classify (Table 2.1).

MODES OF TRANSMISSION

Diseases can be transmitted *directly* or *indirectly*. For example, a disease can be transmitted from person to person (direct transmission) by means of direct contact (as in the case of sexually transmitted infections).

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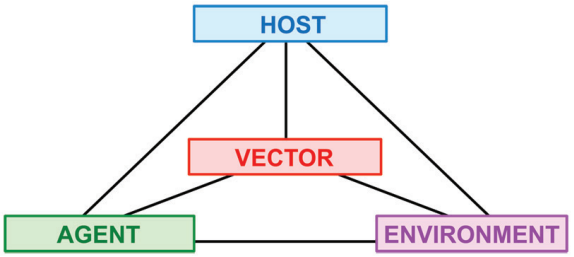

Fig. 2.1 The epidemiologic triad of a disease.

TABLE 2.1 Factors That May Be Associated With Increased Risk of Human Disease

Host Characteristics	Types of Agents and Examples	Environmental Factors
Age	Biologic	Temperature
Sex	Bacteria, viruses	Humidity
Race		Altitude
Religion	Chemical	Crowding
Customs	Heavy metals, alcohol, smoke	Housing
Occupation		Neighborhood
Genetic profile		Water
Marital status	Physical	Milk
Family background	Trauma, radiation, fire	Food
		Radiation
Previous diseases	Nutritional	Air pollution
	Lack, excess	Noise
Immune status		

BOX 2.1 Modes of Disease Transmission

1. Direct
   a. Person-to-person contact
2. Indirect
   a. Common vehicle
      1) Single exposure
      2) Multiple exposures
      3) Continuous exposure
   b. Vector

Indirect transmission can occur through a common vehicle such as a contaminated air or water supply or by a vector such as the mosquito. Some of the modes of transmission are shown in Box 2.1.

Fig. 2.2 is a classic photograph showing droplet dispersal after a sneeze. It vividly demonstrates the potential

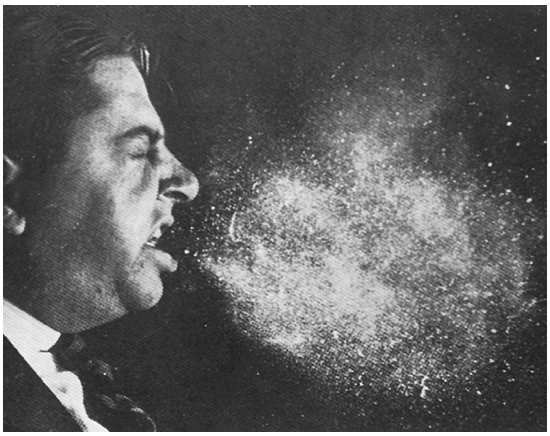

Fig. 2.2 Droplet dispersal following a violent sneeze. (Reprinted with permission from Jennison MW. *Aerobiology*. 17:102, 1947. Copyright 1947 American Association for the Advancement of Science.)

for an individual to infect many people in a brief period of time. As Mims has pointed out:

> *An infected individual can transmit influenza or the common cold to a score of others in the course of an innocent hour in a crowded room. A venereal infection also must spread progressively from person to person if it is to maintain itself in nature, but it would be a formidable task to transmit venereal infection on such a scale.*[2]

Thus, different organisms spread in different ways, and the potential of a given organism for spreading and producing outbreaks depends on the characteristics of the organism, such as its rate of growth, the route by which it is transmitted from one person to another, and the number of susceptible persons in the community.

Fig. 2.3 is a schematic diagram of human body surfaces as sites of microbial infection and shedding. The alimentary tract can be considered as an open tube that crosses the body, and the respiratory and urogenital systems are shown as blind pockets. Each offers an opportunity for infection. The skin is another important portal of entry for infectious agents, primarily through scratches, bites, or injury. Agents that often enter through the skin include streptococci or staphylococci and fungi such as tinea (ringworm). Two points should be made in this regard: first, the skin is not the

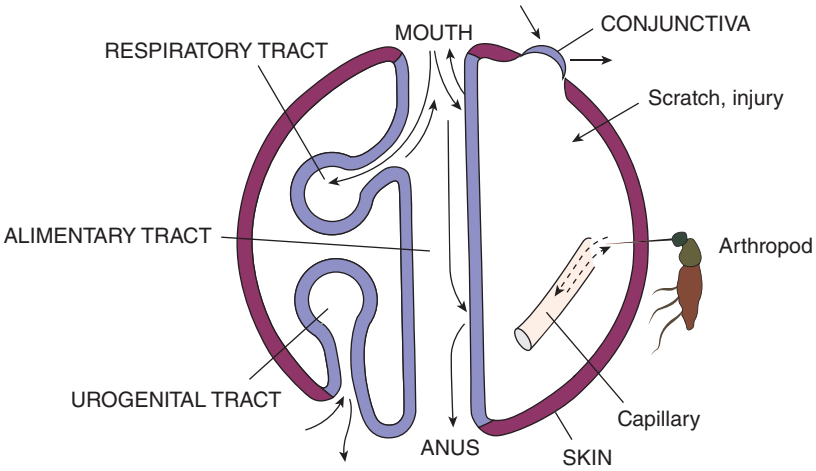

Fig. 2.3 Body surfaces as sites of microbial infection and shedding. (From Mims CA, Nash A, Stephen J. *Mims' Pathogenesis of Infectious Disease*. 5th ed. London: Academic Press; 2001.)

exclusive portal of entry for many of these agents, and second, infections can be acquired through more than one route. The same routes also serve as points of entry for noninfectious disease-causing agents. For example, environmental toxins can be ingested, inspired during respiration, or absorbed directly through the skin. The clinical and epidemiologic characteristics of many infectious and noninfectious conditions often relate to the site of the exposure to an organism or to an environmental substance and to its portal of entry into the body.

Another example of more than one mode of transmission is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of coronavirus disease 19 (COVID-19). While the primary mode of transmission of SARS-CoV-2 is through exposure to respiratory fluids carrying infectious virus by inhalation of air carrying infectious virus, deposition of virus carried in droplets onto exposed mucous membranes or touching infected mucous membranes with hands that were contaminated with droplet-containing infectious virus may occur.[3]

CLINICAL AND SUBCLINICAL DISEASE

It is important to recognize the broad spectrum of disease severity. Fig. 2.4 shows the iceberg concept of disease. Just as most of an iceberg is under water and hidden from view with only its tip visible, so it is with disease: only clinical illness is readily apparent (as seen

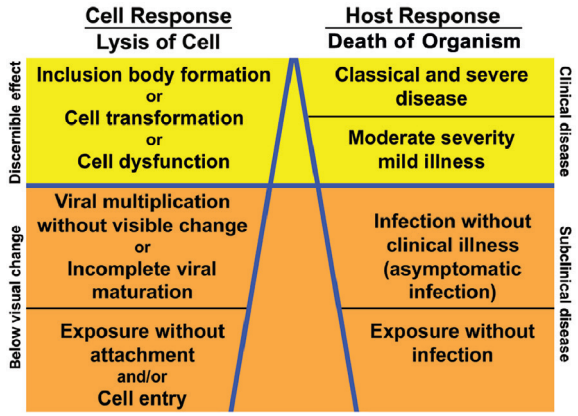

Fig. 2.4 The "iceberg" concept of infectious diseases at the level of the cell and of the host. (Modified from Evans AS, Kaslow RA, eds. *Viral Infections of Humans: Epidemiology and Control*. 4th ed. New York: Plenum; 1997.)

under *Host Response* on the *right* side of Fig. 2.4). However, infections without clinical illness are important, particularly in the web of disease transmission, although they are not clinically apparent. In Fig. 2.4, the corresponding biologic stages of pathogenesis (biologic mechanisms) and disease at the cellular level are seen on the *left*. The iceberg concept is important because it is not sufficient to count only the clinically apparent cases we see; for example, most cases of polio in prevaccine days were subclinical—that is, many people who contracted polio infection were not clinically ill.

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Nevertheless, they were still capable of spreading the virus to others. So too is SARS CoV-2. As a result, we cannot understand and explain the spread of polio or COVID-19 unless the pool of inapparent cases (subclinical) is recognized and tested. From the viewpoint of inapparent disease, this situation is not any different in many noncommunicable diseases. Although these diseases are not spread from person to person, many individuals, for example, can live a long time with inapparent chronic kidney disease, and it is only when they experience a clinical complication that a diagnosis of chronic kidney disease is made.

Fig. 2.5 shows the spectrum of severity for several diseases. Most cases of tuberculosis, for example, are inapparent. However, because inapparent cases can transmit the disease, such cases must be identified and treated to control the further spread of the disease. In measles, many cases are of moderate severity and only a few are inapparent. At the other extreme, without intervention, rabies has no inapparent cases, and most untreated cases are fatal. Thus, we have a spectrum of severity patterns that vary with the disease. Severity appears to be related to the virulence of the organism (how efficient the organism is at producing disease) and to the site in the body where the organism multiplies. All these factors, as well as such host characteristics as the immune response, must be appreciated to understand how disease spreads from one individual to another.

As clinical and biologic knowledge has increased over the years, so has our ability to distinguish different stages of disease. These include clinical and nonclinical disease.

Clinical Disease

Clinical disease is characterized by signs and symptoms.

Nonclinical (Inapparent) Disease

Nonclinical disease may include the following:

1. *Preclinical disease:* Disease that is not yet clinically apparent but is destined to progress to clinical disease.
2. *Subclinical disease:* Disease that is not clinically apparent and is not destined to become clinically apparent. This type of disease is often diagnosed by serologic (antibody) response or culture of the organism.
3. *Persistent (chronic) disease:* A person fails to "shake off" the infection, and it persists for years, at times for life. In recent years, an interesting phenomenon has been the manifestation of symptoms many years after an infection was thought to have been resolved. Some adults who recovered from poliomyelitis in childhood report severe chronic fatigue and weakness; this has been called post-polio syndrome in adult life. These have thus become cases of clinical disease, albeit somewhat different from the initial illness. Long COVID is another example that we have recently identified.
4. *Latent disease:* An infection with no active multiplication of the agent, as when viral nucleic acid is incorporated into the nucleus of a cell as a provirus.

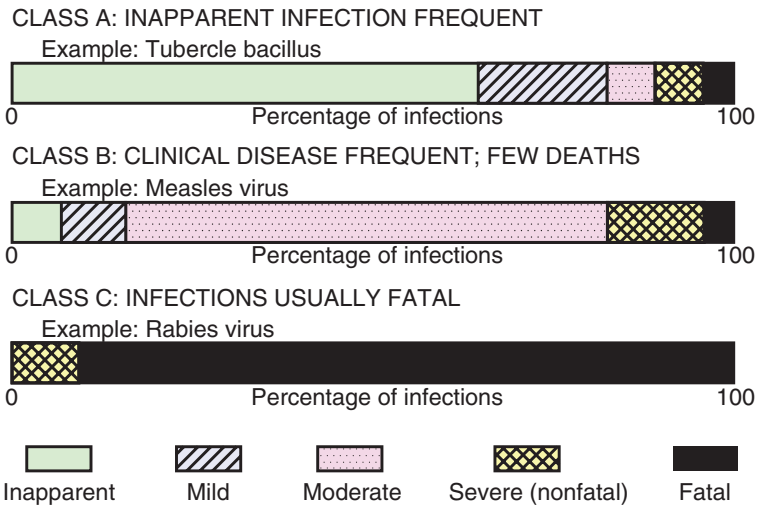

Fig. 2.5 Distribution of clinical severity for three classes of infections (not drawn to scale). (Modified from Mausner JS, Kramer S. *Epidemiology: An Introductory Text*. Philadelphia: WB Saunders; 1985:265.)

In contrast to persistent infection, only the genetic message is present in the host, not the viable organism.

CARRIER STATUS

A carrier is an individual who harbors the organism but is not infected as measured by serologic studies (no evidence of an antibody response) or shows no evidence of clinical illness. This person can still infect others, although the infectivity is generally lower than with other infections. Carrier status may be of limited duration or may be chronic, lasting for months or years. One of the best-known examples of a long-term carrier was Mary Mallon (1869–1938), better known as Typhoid Mary, who carried *Salmonella typhi* and died in 1938. Over a period of many years, she worked as a cook in the New York City area, moving from household to household under different names. She was considered to have caused at least 10 typhoid fever outbreaks that included 51 cases and 3 deaths.

Carrier status also refers to those individuals who have the causative organism without a clinical disease. These can be considered either *asymptomatic* or *presymptomatic*. A contemporary example for this carrier status is those individuals who are harboring SARS-CoV-2 but do not exhibit any symptoms, and subsequently are not tested to detect the virus in their respiratory fluids. Several reports have documented that these individuals can spread infection to others without even knowing that they are transmitting it, and some suggested that the majority of transmission occurs in the *asymptomatic* or *presymptomatic* statuses.[4,5] This becomes of critical importance to public health officials trying to issue guidelines for the public to limit the transmission of disease. Furthermore, it becomes difficult for these individuals with *carrier status* to take proper precautions as they interact with their usual contacts, e.g., isolation, wearing masks, social distancing, etc.

ENDEMIC, EPIDEMIC, AND PANDEMIC

Three other terms must be defined: *endemic, epidemic,* and *pandemic*. *Endemic* is defined as the habitual presence of a disease within a given geographic area. It may also refer to the usual occurrence of a given disease within such an area (sometimes referred to as the "background rate of disease"). *Epidemic* is defined as the occurrence in a community or region of a group of illnesses of similar nature, clearly in excess of normal expectancy and derived from a common or a propagated source (Fig. 2.6). *Pandemic* refers to a worldwide epidemic.

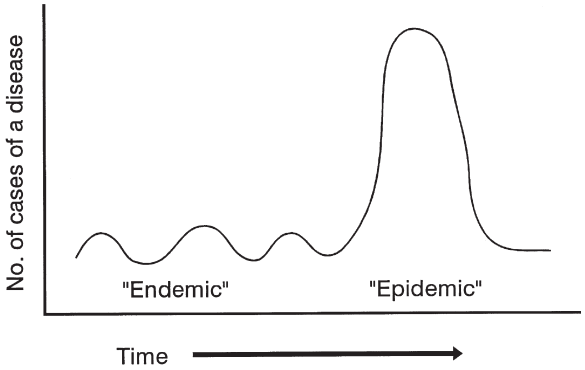

Fig. 2.6 Endemic versus epidemic disease.

How do we know when we have an excess over what is expected? Indeed, how do we know how much to expect? There is no precise answer to either question. Through ongoing surveillance, we may determine what the usual or expected level may be. With regard to excess, sometimes an "interocular test" may be convincing: the difference is so clear that it hits you between the eyes.

Two examples will show how pandemics and fear of pandemics relate to the development of public policy. The first and most recent example is the emergence of SARS-CoV-2, the causative virus of COVID-19 in late 2019. It was initially seen as a mysterious illness that led to pneumonia and death. Given the ease of global transportation, the spread of the infection was exponential. On January 30, 2020, the World Health Organization (WHO) identified COVID-19 as a Public Health Emergency of International Concern, which is the highest level of alarm by the WHO. On March 11, 2020, the WHO formally classified it as a pandemic, and by April 4, 2020, WHO reported that at least 1 million individuals had been identified as a confirmed case of COVID-19—a 10-fold increase in less than a month.[6] Governments across the world imposed travel restrictions, travel bans, shelter-in-place orders, business lockdowns,

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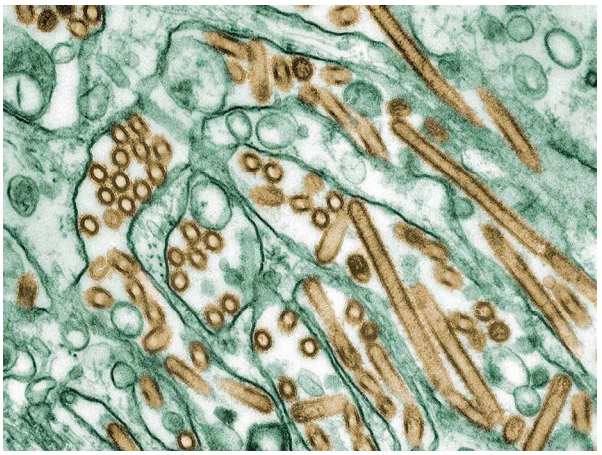

Fig. 2.7 Colorized transmission electron micrograph of avian influenza A H5N1 viruses (seen in *gold*) grown in MDCK cells (seen in *green*). (From Centers for Disease Control and Prevention, Courtesy Cynthia Goldsmith, Jacqueline Katz, and Sherif R. Zaki.)

and school closures to limit the transmission of the disease and reduce the strain on the already-overwhelmed healthcare systems. This was coupled with a worldwide shortage in the availability and even production of personal protective equipment. A recent example of an epidemic is the mpox outbreak in the US which primarily affected bisexual people and men who have sex with men. The mpox epidemic is dramatically reduced from the situation in 2021-2022, in large part because of the vaccinations.

The second example involves an issue that arose in 2011 related to laboratory research into the H5N1, or "bird flu," virus (Fig. 2.7). Although transmission of naturally occurring H5N1 has been primarily limited to persons having direct contact with infected animals, in the unusual cases where people do acquire the infection from animals, the disease is often very severe with a high mortality. There has therefore been serious concern that certain mutations in the virus might increase transmissibility of the virus to humans and could therefore result in a human pandemic. In order to understand fully the possibility of such a mutation and the potential for preventing it, two government-funded laboratories, one at Erasmus Medical Center in the Netherlands and a second at the University of Wisconsin-Madison in the United States, created genetically altered H5N1 strains that could be transmitted between mammals (ferrets) through the air.

After reviewing the two studies, the US National Science Advisory Board for Biosecurity, for the first time in its history, recommended against publishing the details of the methodologies used in these studies. The board cited potential misuse by "*those who would seek to do harm*" by participating in bioterrorist activity. Other scientists, however, including members of an expert panel assembled by the World Health Organization (WHO), disagreed, stating that the work was important to public health efforts to prevent a possible pandemic in humans. In January 2012, a moratorium on some types of H5N1 research was self-imposed by the researchers to allow time for discussion of these concerns by experts and by the public. The results of the two studies were subsequently published in May and June of 2012.[7–9]

The major unresolved issue is whether the potential benefits to society from the results of these types of studies outweigh the risks from the uncontrolled spread of mutated virus, resulting from either lapse in biosafety in the laboratory (accidental release of the virus) or bioterrorist activity (intentional release of the virus). Scientists and policy makers are obliged to develop methods for assessing the risks and benefits of conducting different types of experimental research. In addition, these events illustrate that censorship and academic freedom in science remain highly relevant issues today.

DISEASE OUTBREAKS

Let us assume that a food becomes contaminated with a microorganism. If an outbreak occurs in the group of people who have eaten the food, it is called a *common-vehicle exposure*, because all the cases that occurred were in persons exposed to the suspected contaminated food. The food may be served only once—for example, at a catered luncheon—resulting in a *single exposure* to the people who eat it, or the food may be served more than once, resulting in *multiple exposures* to people who eat it more than once. When a water supply is contaminated with sewage because of leaky pipes, the contamination can be either *periodic*, causing multiple exposures as a result of changing pressures in the water supply system, which may cause intermittent contamination, or *continuous*, in which case a constant leak leads to persistent

contamination. The epidemiologic picture that is manifested depends on whether the exposure is single, multiple, or continuous.

For purposes of this discussion, we will focus on the *single-exposure, common-vehicle outbreak* because the issues discussed are most clearly seen in this type of outbreak. What are the characteristics of such an outbreak? First, such outbreaks are generally explosive—that is, there is a sudden and rapid increase in the number of cases of the disease or condition in a population. (Interestingly, single-exposure common-vehicle epidemics of noncommunicable diseases, such as the epidemic of leukemia following the explosion of an atomic bomb in Hiroshima and Nagasaki, also seem to follow the same pattern.) Second, the cases are limited to people who share the common exposure. This is self-evident, because in the first wave of cases we would not expect the disease to develop in people who were not exposed unless there was another independent source of the disease in the community. Third, in a food-borne outbreak, cases rarely occur in persons who did not eat the food—that is, those who acquire the disease from a primary case who ate the food. The reason for the relative rarity of such secondary cases in this type of outbreak is not well understood.

In the United States, the leading cause of food-borne–related illness is contamination with norovirus (from the Norwalk virus family). Globally, norovirus results in a total of $4.2 billion in direct health care system costs and $60.3 billion in societal costs per year.[10]

Over recent decades, a growing number of outbreaks of acute gastroenteritis (AGE) have occurred aboard cruise ships. The Centers for Disease Control and Prevention (CDC) has reported that rates of AGE among passengers on cruise ships have decreased from 27.2 cases per 100,000 travel days in 2008 to 22.3 in 2014, while the rate among crew members was essentially unchanged.[11] This could potentially be attributed to the production of operational manuals or specific guidelines providing hygiene standards, increasing awareness among passengers and crew members, communicable disease surveillance programs, and preventive procedures in addition to regulatory enforcement and strict inspections through the CDC's Vessel Sanitation Program (VSP), which monitors outbreaks on cruise ships and works to prevent

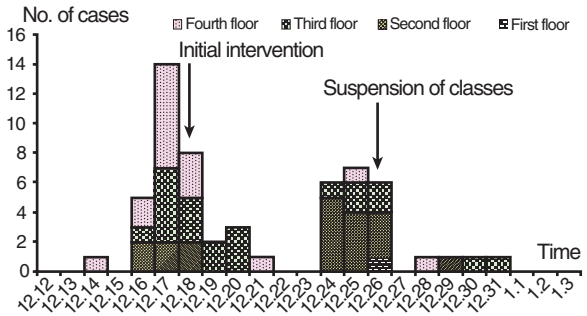

Fig. 2.8 Distribution of cases grouped by floor and by date of outbreak onset in a school in the province of in Jiangsu Province, China, in 2014. (From Shi C, Feng W-H, Shi P et al. An acute gastroenteritis outbreak caused by GII.17 norovirus in Jiangsu Province, China. *Int J Infect Dis*. 2016;49:30-32.)

and control transmission of illness aboard these ships. (Data from each outbreak are available on their website, http://www.cdc.gov/nceh/vsp/.) In areas with a high prevalence of norovirus, particularly the recombinant GII.2 type, such as in the provinces of Guangdong and Jiangsu, China, outbreaks of AGE continue to occur frequently.[12] For example, on December 14, 2014, a student in third grade vomited in the classroom and washroom several times and was considered the earliest suspected case of norovirus. Over the following 3 days, 27 more cases were reported, which were mainly located on the fourth floor (12 cases) and third floor (9 cases) of the school building. Fig. 2.8 shows the epidemic curve with the number of cases each day. The first peak of the outbreak was on December 17, which was starting to taper off when implementation of control measures such as quarantine and disinfection were followed. However, a few days later, on December 25, the attack rate peaked again, with cases occurring mainly on the second floor (12 cases) and third floor (5 cases). In order to aggressively contain the outbreak, the school was closed temporarily, and the outbreak came to an end on December 31.

IMMUNITY AND SUSCEPTIBILITY

The amount of disease in a population depends on a balance between the number of people in that population who are susceptible and therefore at risk for the disease and the number of people who are not susceptible or

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immune and therefore not at risk. They may be immune because they have had the disease previously (and have antibodies) or because they have been immunized. They also may not be susceptible on a genetic basis. Clearly if the entire population is immune, no epidemic can develop. But the balance is usually struck somewhere in between immunity and susceptibility, and when it moves toward susceptibility, the likelihood of an outbreak increases. This has been observed particularly in formerly isolated populations who were later exposed to disease. For example, in the 19th century, Panum observed that measles occurred in the Faroe Islands in epidemic form when infected individuals entered the isolated and susceptible population.[13] In another example, severe outbreaks of streptococcal sore throats developed when new susceptible recruits arrived at the Great Lakes Naval Station.[14]

HERD IMMUNITY

Herd immunity is defined as the resistance of a group of people to an attack by a disease to which a large proportion of the members of the group are immune. If a large percentage of the population is immune, the entire population is likely to be protected, not just those who are immune. Why does herd immunity occur? It happens because disease spreads from one person to another in any community. Once a certain proportion of people in the community are immune, the likelihood is small that an infected person will encounter a susceptible person to whom he can transmit the infection; more of his encounters will be with people who are immune. The presence of a large proportion of immune persons in the population lessens the likelihood that a person with the disease will encounter a susceptible individual.

Why is the concept of herd immunity so important? When we carry out immunization programs, it may not be necessary to achieve 100% immunization rates to immunize the population successfully. We can achieve highly effective protection by immunizing a large part of the population; the remaining part will be protected because of herd immunity.

For herd immunity to exist, certain conditions must be met. The disease agent must be restricted to a single host species within which transmission occurs, and that transmission must be relatively direct from one member of the host species to another. If we have a reservoir in which the organism can exist outside the human host, herd immunity will not operate because other means of transmission may be available. In addition, infections must induce solid immunity. If immunity is only partial, we will not build up a large proportion of immune people in the community.

What does this mean? Herd immunity operates if the probability of an infected person encountering every *other individual* in the population ("random mixing") is the same. But if a person is infected and all his or her interactions are with people who are susceptible (i.e., there is no random mixing of the population), he or she is likely to transmit the disease to other susceptible people. Herd immunity operates optimally when populations are constantly mixing. This is a theoretical concept because, obviously, populations are never completely randomly mixed. All of us associate with family and friends, for example, more than we do with strangers. However, the degree to which herd immunity is achieved depends on the extent to which the population approaches a random mixing. Thus, we can interrupt the transmission of disease even if not everyone in the population is immune if a critical percentage of the population is immune.

What percentage of a population must be immune for herd immunity to operate? This percentage varies from disease to disease. For example, in the case of measles, which is highly communicable, it has been estimated that 94% of the population must be immune before the chain of transmission is interrupted. With decreasing childhood immunization rates in the United States associated with parental concerns regarding the risk of autism spectrum disorder, measles outbreaks are becoming more common. A total of 125 measles cases with rash occurred in a 6-week period; among these cases 110 were California residents (45% unvaccinated), of whom 35% had visited one or both Disney theme parks between December 17 and 20, 2014, the suspected source of exposure. Of the secondary cases, most (26/34) were close contacts. An additional 15 cases associated with the Disney theme parks were reported in seven additional states.[15]

Let us now consider poliomyelitis immunization and herd immunity. From 1951 to 1954, an average of 24,220 cases of paralytic poliomyelitis occurred in the United States each year. Two types of vaccine are available. The oral polio vaccine (OPV) protects not only

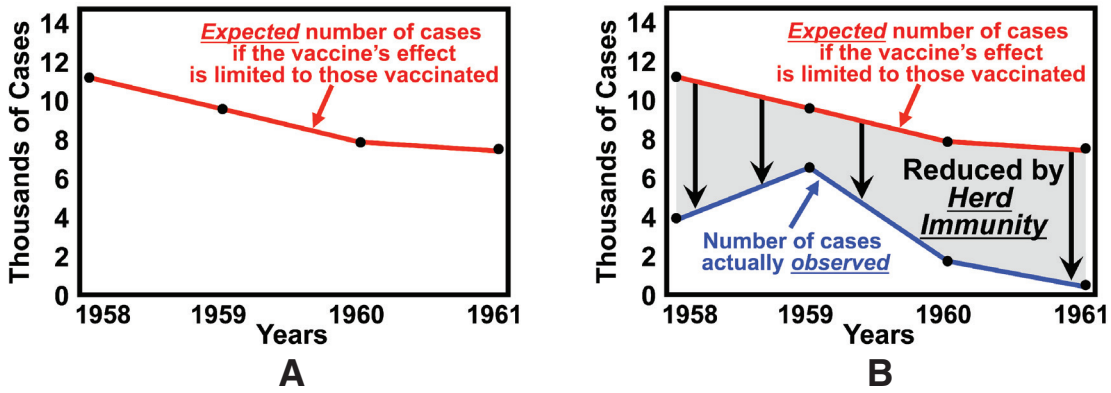

Fig. 2.9 Effect of herd immunity, United States, 1958–61. **(A)** Expected number of paralytic poliomyelitis cases if the vaccine's effect was limited to vaccinated people. **(B)** Number of cases observed as a result of herd immunity. (Modified from American Academy of Pediatrics News. Copyright 1998. From Stickle G. Observed and expected poliomyelitis in the United States, 1958–1961. *Am J Public Health*. 1964;54:1222-1229.)

those who are vaccinated but also others in the community through secondary immunity, produced when the vaccinated individual spreads the active vaccine virus to contacts. In effect, the contacts are immunized by the spread of virus from the vaccinated person. If enough people in the community are protected in this way, the chain of transmission is interrupted. However, even inactivated poliovirus vaccine (IPV), which does not produce secondary immunity (does not spread the virus to susceptible contacts), can produce herd immunity if enough of the population is immunized. Even those who are not immunized will be protected because the chain of transmission in the community has been interrupted.

From 1958 to 1961, only IPV was available in the United States. Fig. 2.9A shows the expected number of cases each year if the vaccine had protected only those who received the vaccine. Fig. 2.9B shows the number of polio cases observed. Clearly far fewer cases occurred than would have been expected from the direct effects of the vaccine alone. The difference between the two curves represents the effect of herd immunity from the vaccine. Thus, nonimmunized individuals can gain some protection from either the OPV or IPV.

INCUBATION PERIOD

The incubation period is defined as the *interval from receipt of infection to the time of onset of clinical illness* (the onset of recognizable symptoms). If you become infected today, the disease with which you are infected may not develop for several days or weeks. During this time, the *incubation period*, you feel completely well and show no signs of the disease.

Why does disease not develop immediately at the time of infection? What accounts for the incubation period? It may reflect the time needed for the organism to replicate sufficiently until it reaches the critical mass needed for clinical disease to result. It probably also relates to the site in the body at which the organism replicates—whether it replicates superficially, near the skin surface, or deeper in the body (e.g., in the gut). The dose of the infectious agent received at the time of infection may also influence the length of the incubation period. With a large dose, the incubation period may be shorter.

In the case of the COVID-19 pandemic, the incubation period was estimated to be 6.5 days from exposure to symptom onset.[16] However, it was shown that the mean incubation period during the Delta and Omicron variants have shorter incubation periods of 3–4 days.[17–19] The knowledge of the incubation period has significant clinical implication on the diagnosis, management, and public health response to exposure to positive cases with COVID-19.

The incubation period is also of historical interest because it is related to what may have been the only medical advance associated with the Black Death (plague) in Europe. In 1374, when people were terribly

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frightened of the Black Death, the Venetian Republic appointed three officials who were responsible for inspecting all ships entering the port and for excluding ships that had sick people on board. It was hoped that this intervention would protect the community. In 1377, in the Italian seaport of Ragusa, travelers were detained in an isolated area for 30 days *(trentini giorni)* after arrival to see whether infection developed. This period was found to be insufficient, and the period of detention was lengthened to 40 days *(quarante giorni)*. This is the origin of the word *quarantine*.

How long would we want to isolate a person? We would want to isolate a person until he or she is no longer infectious to others (having passed through the suspected incubation period). When a person is clinically ill, we generally have a clear sign of potential infectiousness. An important problem arises *before* the person becomes clinically ill—that is, during the incubation period. If we knew when he or she became infected and knew the general length of the incubation period for the disease, we would want to isolate the infected person during this period (and perhaps a few days extra to be especially cautious) to prevent transmission of the disease to others. In most situations, however, we do not know that a person has been infected, and we may not know until signs of clinical disease become manifest. In addition, we may not know the distribution of the incubation period.

This leads to an important question: is it worthwhile to isolate a patient, such as a child with chickenpox? The problem is that, during at least part of the incubation period, when the person is still free of clinical illness, he or she can transmit the disease to others. Thus, we have people who are not (yet) clinically ill but who have been infected; they are unaware of their infection status and are able to transmit their disease. For many common childhood diseases, by the time clinical disease develops in the child, he or she has already transmitted the disease to others. Therefore, isolating such a person at the point at which he or she becomes clinically ill will not necessarily be effective. On the other hand, isolation can be very valuable. In September 2012, health officials in Saudi Arabia first reported a severe acute respiratory illness with symptoms of fever, cough, and shortness of breath. The causative organism was shown to be the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which has an incubation period of about 5 or 6 days. MERS-CoV likely came from infected camels in the Arabian Peninsula and spread through person-to-person close contact, with health care personnel at higher risk of infection if universal precautions were not adhered to. All MERS-CoV cases that have been identified had a positive history of someone living in or traveling to countries in or near the Arabian Peninsula. Another outbreak of MERS-CoV occurred in the Republic of Korea in 2015 and was also linked to a returning traveler from the Arabian Peninsula. As of May 2017, WHO has reported that there had been 1952 laboratory-confirmed cases of infection with MERS-CoV from 27 countries, of whom 693 (36%) had died.

Fig. 2.10 shows the epidemic curve of weekly trends in number of COVID-19 cases in the US reported to the CDC from early 2020 to late 2022. (Note that, unlike the epidemic curve for common vehicle epidemics, the curve for person-to-person spread is multimodal.) While the first outbreak occurred in Wuhan, China, most probably in December 2019, every country around the world reported cases of COVID-19 within a few weeks.

Different diseases have different incubation periods. A precise incubation period does not exist for a given disease; rather, a range of incubation periods is characteristic of that disease. Fig. 2.11 shows the range of incubation periods for several diseases. In general, the length of the incubation period is a characteristic of the infective organism.

The incubation period for infectious diseases has its analogue in noninfectious diseases. Thus, even when an individual is exposed to a carcinogen or other environmental toxin, the disease is often manifest only after months or even years. For example, mesothelioma resulting from asbestos exposure may occur 20 to 30 years after the exposure. The incubation period for noninfectious diseases is often referred to as the *latency period*.

Fig. 2.12 is a graphic representation of an outbreak of *Salmonella typhimurium* at a medical conference in Wales in 1986. Each bar represents the number of cases of disease developing at a certain point in time after the exposure; the number of hours since exposure is shown along the horizontal axis. If we draw a line connecting the tops of the bars, it is called the *epidemic curve*, which is defined as the distribution of the times of onset of the disease. In a *single-exposure, common-vehicle epidemic,* the epidemic curve represents the distribution of the

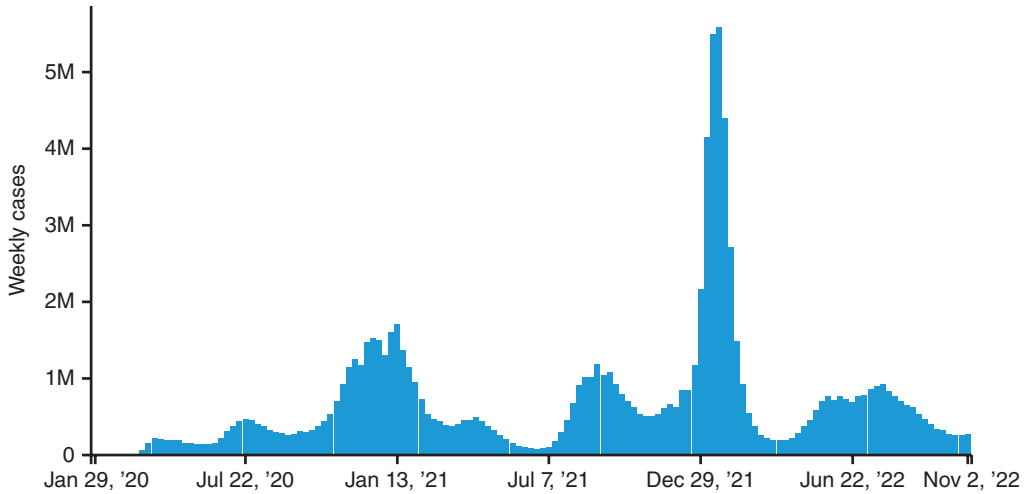

Fig. 2.10 Weekly trends in number of Covid-19 cases in the United States reported to the CDC. (From Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, November 7. https://covid.cdc.gov/covid-data-tracker.)

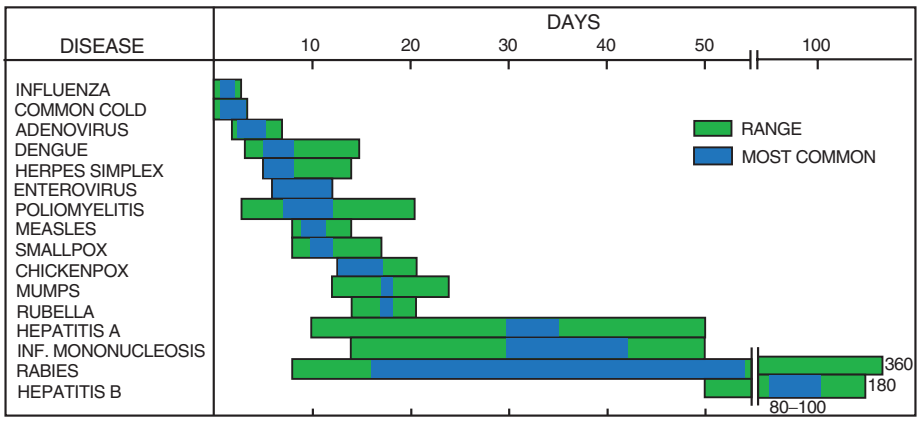

Fig. 2.11 Incubation periods of viral diseases. *INF.,* Infectious. (From Evans AS, Kaslow RA, eds. *Viral Infections of Humans: Epidemiology and Control.* 4th ed. New York: Plenum; 1997.)

incubation periods. This should be intuitively apparent: if the infection took place at one point in time, the interval from that point to the onset of each case is the incubation period in that person.

As seen in Fig. 2.12, involving *Salmonella typhimurium*, there was a rapid, explosive rise in the number of cases within the first 16 hours, which suggests a single-exposure, common-vehicle epidemic. In fact, this pattern is the classic epidemic curve for a single-exposure common-vehicle outbreak (Fig. 2.13, *left*). The reason for this configuration is not known, but it has an interesting property: if the curve is plotted against the logarithm of time rather than against time itself, the curve becomes a normal curve, which has useful statistical properties (see Fig. 2.13, *right*). If plotted on log-normal graph paper, we obtain a straight line, and estimation of the median incubation period is facilitated. Armenian and Lilienfeld[20] showed that a log-normal curve is also typical of single-exposure common-vehicle epidemics of noninfectious diseases.

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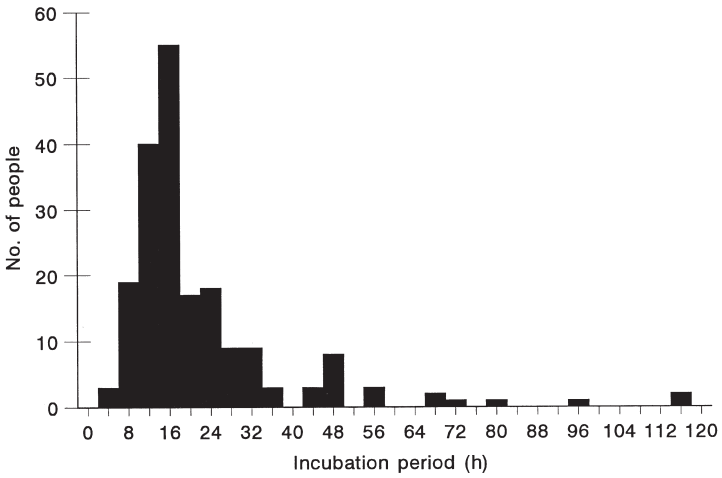


Fig. 2.12 Incubation periods for 191 delegates affected by a *Salmonella typhimurium* outbreak at a medical conference in Wales, 1986. (Modified from Glynn JR, Palmer SR. Incubation period, severity of disease, and infecting dose: evidence from a *Salmonella* outbreak. *Am J Epidemiol*. 1992;136:1369-1377.)

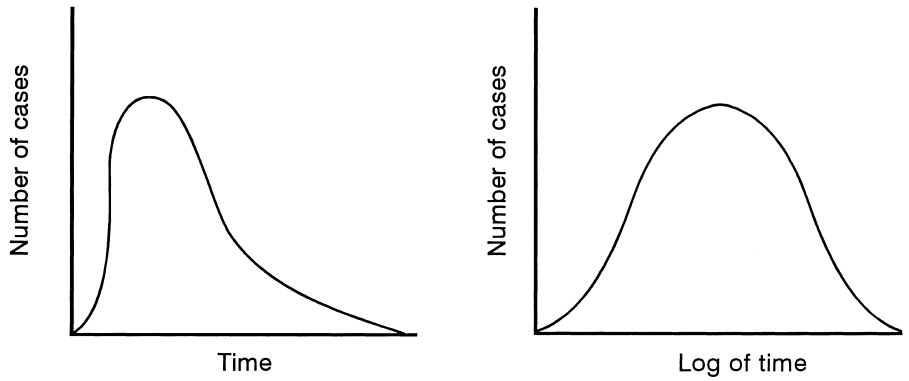


Fig. 2.13 Number of cases plotted against time and against the logarithm of time.

The three critical variables in investigating an outbreak or epidemic are as follows:

1. When did the exposure take place?
2. When did the disease begin?
3. What was the incubation period for the disease?

If we know any two of these, we can calculate the third.

ATTACK RATE

An attack rate is defined as:

$$\frac{\text{Number of people at risk in whom a certain illness develops}}{\text{Total number of people at risk}}$$

The attack rate is useful for comparing the risk of disease in groups with different exposures. The attack rate can be specific for a given exposure. For example, the attack rate in people who ate a certain food is called a *food-specific attack rate*. It is calculated by:

$$\frac{\text{Number of people who ate a certain food and became ill}}{\text{Total number of people who ate that food}}$$

In general, *time* is not explicitly specified in an attack rate because the exposure is common and the illness is acute—given what is usually known about how long after an exposure most cases develop, the time period is implicit in the attack rate.

A person who acquires the disease from that exposure (e.g., from a contaminated food) is called a *primary case*. A person who acquires the disease from exposure to a primary case is called a *secondary case*. The *secondary attack rate* is therefore defined as the attack rate in susceptible people who were not exposed to the suspected agent who have been exposed to a primary case. It is a good measure of person-to-person spread of disease after the disease has been introduced into a population, and it can be thought of as a ripple moving out from the primary case. We often calculate the secondary attack rate in family members of the index case.

The secondary attack rate also has application in noninfectious diseases when family members are examined to determine the extent to which a disease clusters among first-degree relatives of an index case (heritability or clustering within families), which may yield a clue regarding the relative contributions of genetic and environmental factors to the cause of a disease (think of secondary tobacco exposure and lung cancer in non-smokers).

EXPLORING OCCURRENCE OF DISEASE

The concepts outlined in this chapter form the basis for exploring the occurrence of disease. When a disease appears to have occurred at more than an endemic (usual) level and we wish to investigate its occurrence, we ask:

Who was attacked by the disease?

When did the disease occur?

Where did the cases arise?

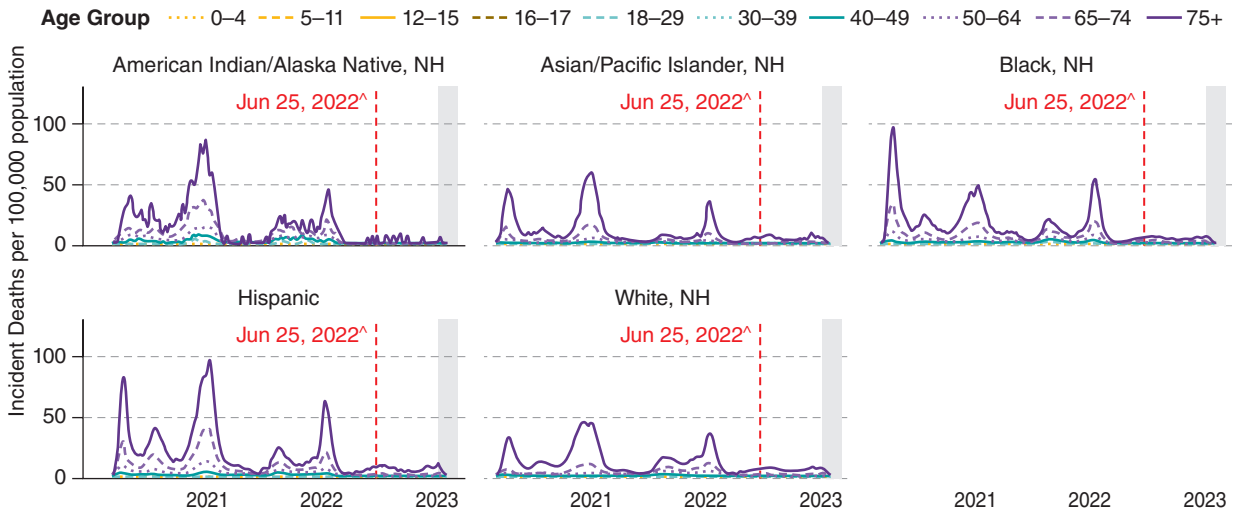
It is well known that disease risk is affected by all these factors.

Who?

The characteristics of the human host are clearly related to disease risk. Factors such as sex, age, and race/ethnicity as well as behavioral risk factors (e.g., smoking) may have major effects.

COVID-19

Fig. 2.14 shows the COVID-19 weekly deaths per 100,000 population by age and race/ethnicity in the US



US: Includes data up to the week ending on Feb 04, 2023. Percentage of deaths among reported cases - 0.97%. Percentage of deaths reporting race and age by date - 83.71%.
US territories are included in case and death counts but not in population counts. Potential six-week delay in case reporting to CDC denoted by gray bars. Weekly data with five or fewer deaths have been suppressed. *Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC. The date for the current week extends through Saturday. ^The death rate for Texas during the week ending Jun 25, 2022, are reflective of a data reporting artifact.
Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public Health Science Team

Fig 2.14 COVID-19 weekly deaths per 100,000 population by age group and race/ethnicity, United States, March 01,2020–February 04, 2023.* (From Centers for Disease Control and Prevention. Covid Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2023, February 4. https://covid.cdc.gov/covid-data-tracker).

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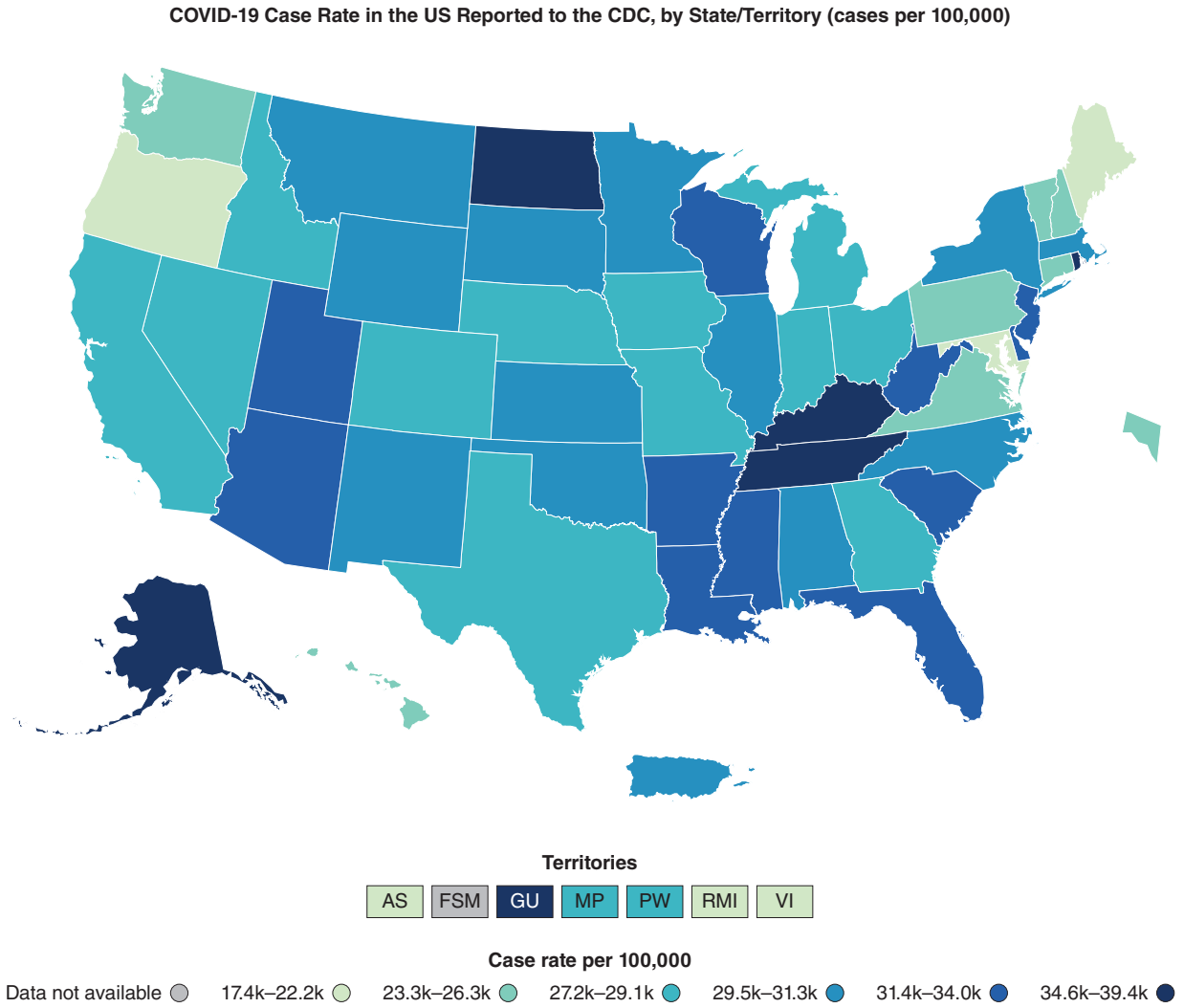

Fig 2.15 COVID-19 case rate in the US reported to the CDC, by state/territory (cases per 100,000). (From Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: US Department of Health and Human Services, CDC; 2022, November 07. https://covid.cdc.gov/covid-data-tracker.)

from March 2020 to October 2022.[21] There is a clear disparity in the incident deaths per 100,000 population for the highest age group (75+ years), followed by those aged 65–74 years, compared with younger age groups. This is particularly evident in the first wave of the pandemic, and every wave of COVID-19 thereafter. On the other hand, there was geographical distribution of the COVID-19 cases throughout the US from the beginning of the pandemic. Fig. 2.15 shows COVID-19 case rates in the US reported to the CDC, by state/territory (cases per 100,000).[21] Alaska, Kentucky, North Dakota, Tennessee, and West Virginia had the highest case rates in the US, while Maine, Maryland, Oregon, Vermont, and Washington had the lowest case rates.

Gonorrhea

As shown in Fig. 2.16, rates of gonorrhea have historically been higher in males than in females, and this sex difference is observed at least as far back as 1960 (not shown in this graph). Because women are more likely

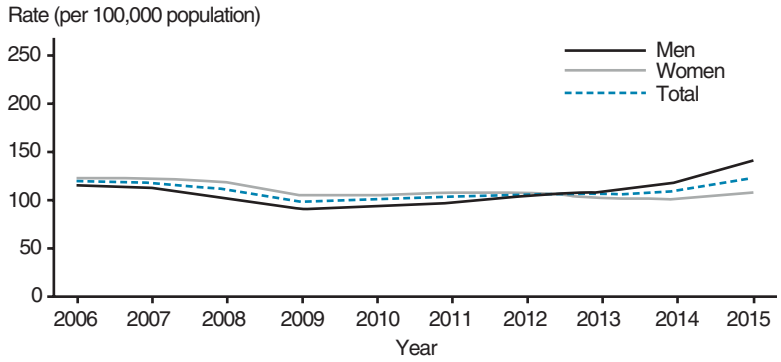

Fig. 2.16 Gonorrhea—rates of reported cases by sex, United States, 2006–15. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2010*. Atlanta: US Department of Health and Human Services; 2016. https://www.cdc.gov/std/stats15/figures/13.htm. Accessed May 8, 2017.)

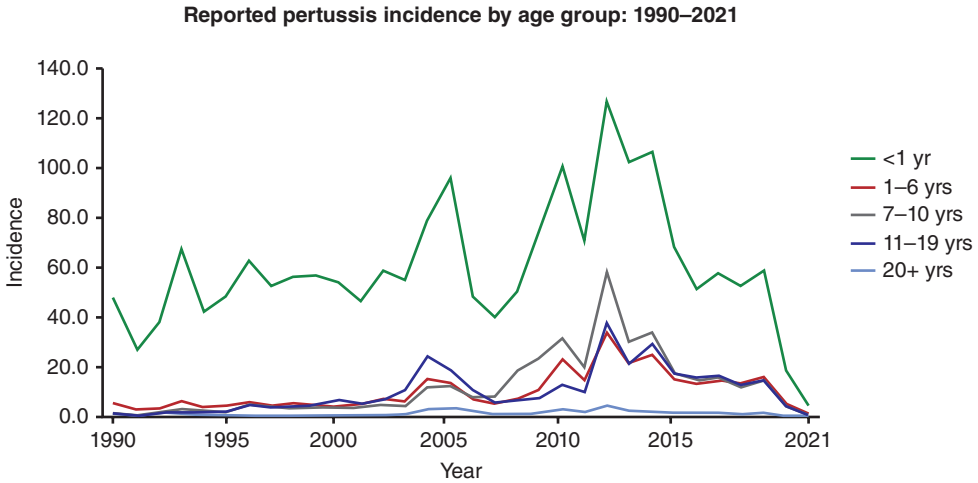

Fig. 2.17 Pertussis (whooping cough) incidence per 100,000 population by year and age group, United States, 1990–2021. (From Centers for Disease Control and Prevention. Pertussis (Whooping Cough): Surveillance and Reporting. https://www.cdc.gov/pertussis/surv-reporting.html. Accessed July 9, 2023.)

to be asymptomatic, the disease in women has probably been underreported. Rates had been leveling off in both men and women over the past few decades, but since 2013, higher rates of gonorrhea have been observed in men than in women. Such increases in rates among men could be either attributed to increased transmission or increased case ascertainment (e.g., through increased extragenital screening) among gay, bisexual, and other men who have sex with men.

Pertussis

The incidence of pertussis ("whooping cough") in the United States peaked in 2004 when the rate reached 8.9 cases per 100,000 population, more than twice that reported in 2003. In 1994, the rate was 1.8. The number of cases in 2004 was the highest reported since 1959. Although childhood pertussis vaccine coverage is high in the United States, pertussis continues to cause morbidity. Some of this increase may result from improved diagnostics as well as recognition and reporting of cases. As seen in Fig. 2.17, the lowest rates for pertussis in the United States were observed in 1991. Although incidence rates showed two more peaks in 2008 and 2009, they subsequently declined until 2016. Of note, infants aged less than 1 year, who are at the greatest risk for death, continue to have the highest reported rate of pertussis.

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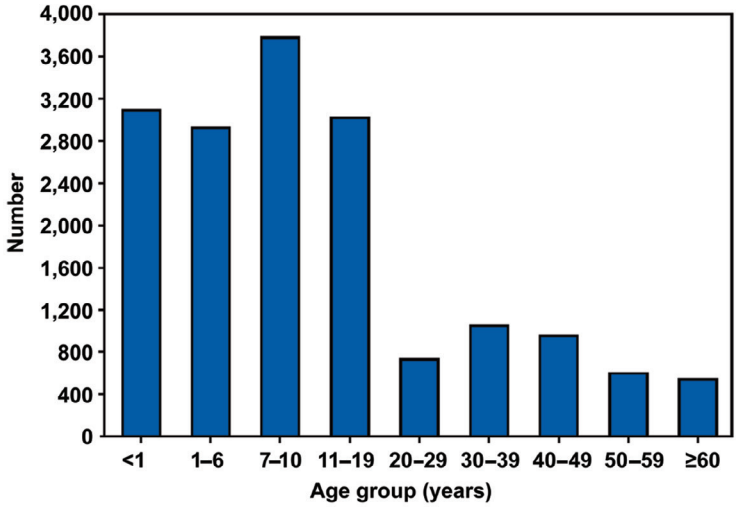

Fig. 2.18 Pertussis (whooping cough), reported numbers of cases by age group, United States, 2009. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2009. *Morb Mortal Wkly Rep.* 2011;58:1-100.)

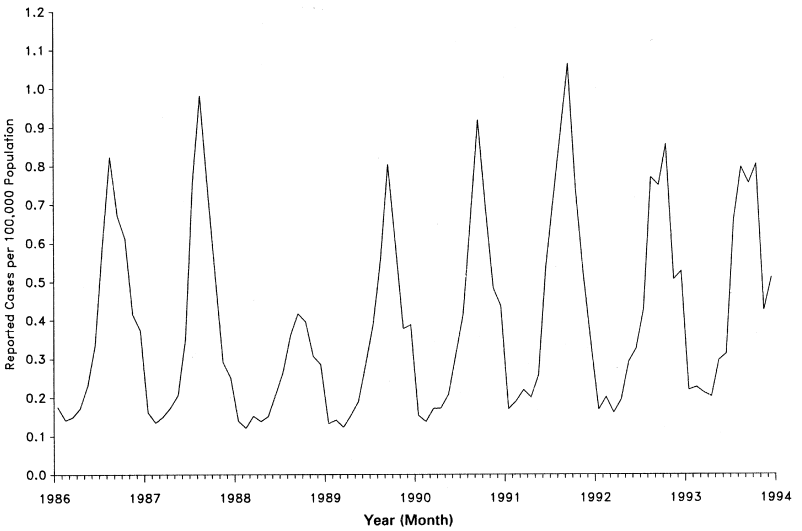

Fig. 2.19 Aseptic meningitis, reported cases per 100,000 population by month, United States, 1986–93. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1993. *Morb Mortal Wkly Rep.* 1994;42:22.)

Pertussis occurrence is clearly related to age (Fig. 2.18). Although the highest *rate* of pertussis was in infants less than 6 months of age (99 per 100,000 population), the *number* of reported cases was highest in children ages 11 to 19. Approximately half of reported pertussis cases in 2014 and 2015 occurred in 10- to 19-year-olds and in adults over the age of 20 years. Although the specific cause of this phenomenon is unknown, it could result from a waning of protection 5 to 10 years after pertussis immunization.

When?

Certain diseases occur with a certain periodicity. For example, aseptic meningitis peaks at consistent yearly rates (Fig. 2.19). Often, there is a seasonal pattern to the temporal variation. For example, diarrheal disease is

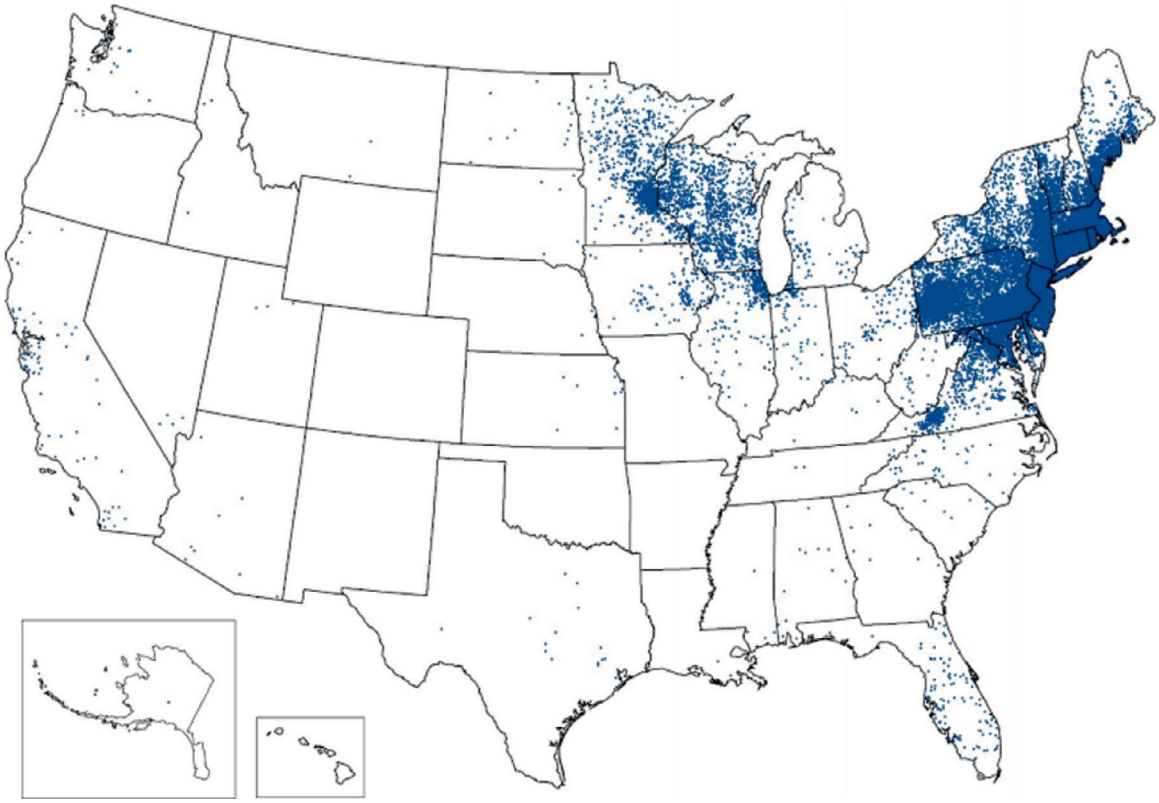

Fig. 2.20 Reported cases of Lyme disease—United States, 2015. Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. People travel between states, and the place of residence is sometimes different from the place where the patient became infected. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2015. https://www.cdc.gov/lyme/resources/reportedcasesoflymedisease_2015.pdf. Accessed May 8, 2017.)

most common during the summer months, and respiratory disease is most common during the winter months. The question of *when* is also addressed by examining trends in disease incidence over time. For example, in the United States, both the incidence of and deaths from acquired immunodeficiency syndrome (AIDS) increased for many years, but it began to decline in 1996, largely as a result of the new combination of highly active antiretroviral therapy and health education efforts.

Where?

Disease is not randomly distributed in time or place. For example, Fig. 2.20 shows the geographic distribution of Lyme disease in the United States in 2015, with each dot representing one case of Lyme disease. There is a clear clustering of cases along the Northeast coast, in the north-central part of the country, and in the Pacific Coast region. The states in which established enzootic cycles of *Borrelia burgdorferi*, the causative agent, have been reported accounted for 95% of the cases. The distribution of the disease closely parallels that of the deer tick vector.

A dramatic example of spread of disease is seen with West Nile virus (WNV) in the United States.[22] WNV was first isolated and identified in 1937 in the West Nile region of Uganda, and for many years it was found only in the Eastern Hemisphere. The basic cycle of the disease is bird-mosquito-bird. Mosquitoes become infected when they bite infected birds. When mosquitoes that bite both birds and humans become infected, they

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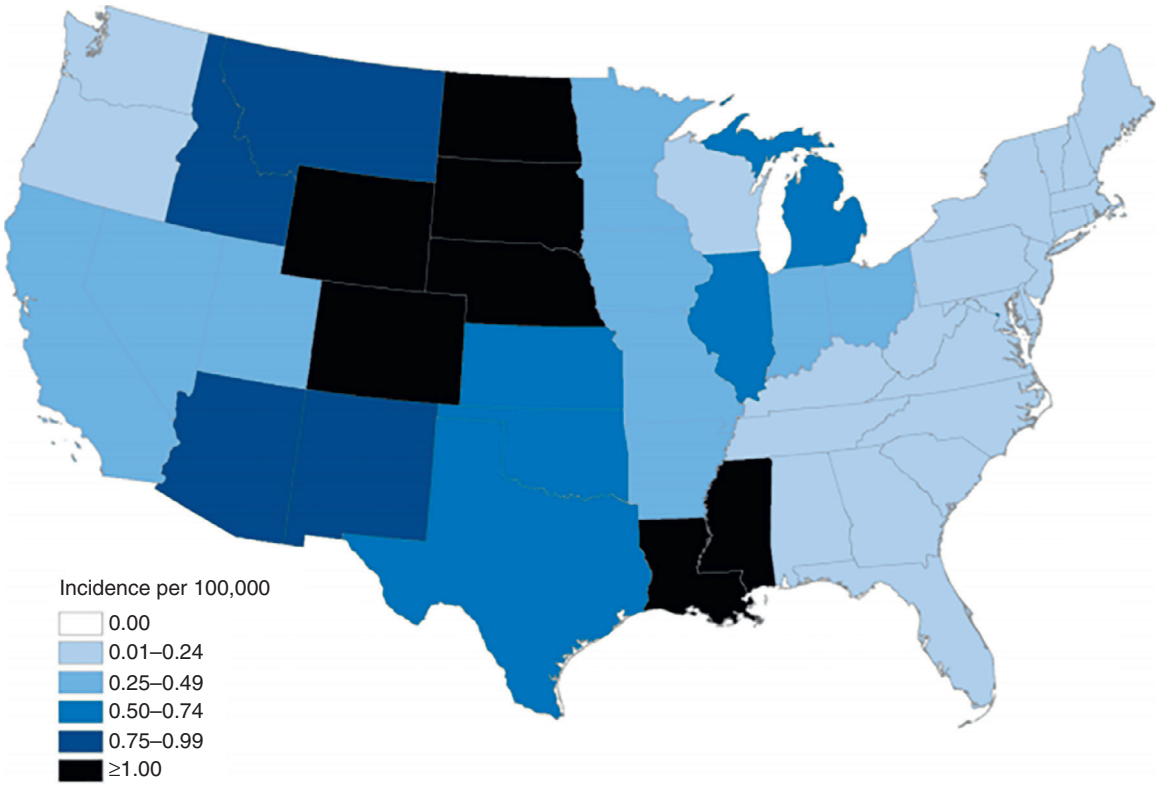

Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

Fig. 2.21 Average annual incidence of West Nile virus neuroinvasive disease reported to the Centers for Disease Control and Prevention by state, 1999–2015. (From Centers for Disease Control and Prevention. https://www.cdc.gov/westnile/resources/pdfs/data/6-WNV-Neuro-Incidence-by-State-Map_1999-2015_07072016.pdf. Accessed May 8, 2017.)

pose a threat to people. Most human infections are subclinical, but approximately 1 of 150 infections in recent years has resulted in meningitis or encephalitis. The risk of neurologic disease is significantly increased in people older than 50 years of age. Other symptoms include fever, nausea and vomiting, rash, headache, and muscle weakness. The case-fatality rate, or the proportion of people who develop the disease (cases) who then die of the disease, can be as high as 14%. Advancing age is a major risk factor for death from WNV, with one study reporting death nine times as frequently in older compared with younger patients. Treatment is supportive, and prevention is largely addressed through mosquito control and the use of insect repellents and bed nets. Tracking the distribution of the disease depends on surveillance for human cases and on monitoring birds and animals for the disease and deaths from the disease. Surveillance is discussed in further detail in Chapter 3.

WNV was first identified in New York City in 1999. Fig. 2.21 shows the average annual incidence of WNV neuroinvasive disease reported to the CDC by states from 1999 to 2015. During the same reporting period, the WNV disease epidemic peaked during the month of September every year (Fig. 2.22). Much remains to be learned about this disease to facilitate treatment, prevention, and control.

OUTBREAK INVESTIGATION

The characteristics just discussed are the central issues in virtually all outbreak investigations. The steps for

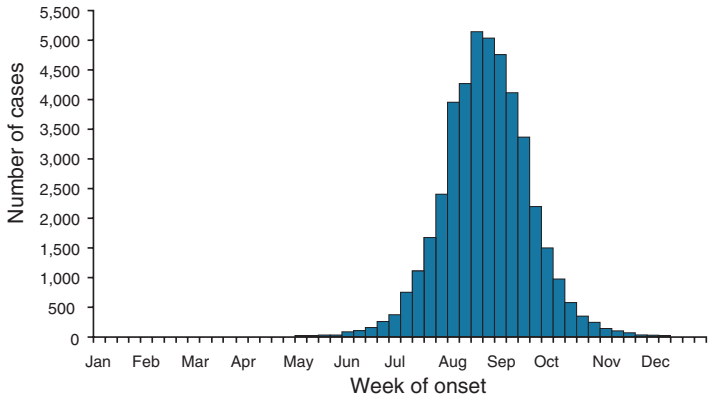

Fig. 2.22 Number of West Nile virus disease cases reported to the Centers for Disease Control and Prevention by week of illness onset, 1999–2015. (From Centers for Disease Control and Prevention. https://www.cdc.gov/westnile/resources/pdfs/data/4-WNV-Week-Onset_for-PDF_1999-2015_07072016.pdf. Accessed May 8, 2017.)

BOX 2.2 Steps in Investigating an Acute Outbreak

Investigating an acute outbreak may be primarily deductive (i.e., reasoning from premises or propositions proved previously) or inductive (i.e., reasoning from particular facts to a general conclusion), or it may be a combination of both.

Important considerations in investigating an acute outbreak of infectious diseases include determining that an outbreak has in fact occurred and defining the extent of the population at risk, determining the measure of spread and reservoir, and characterizing the agent.

Steps commonly used are listed below, but depending on the outbreak, the exact order may differ.

1. Define the outbreak and validate the existence of an outbreak
   - a. Define the "numerator" (cases)
     - 1) Clinical features: Is the disease known?
     - 2) What are its serologic or cultural aspects?
     - 3) Are the causes partially understood?
   - b. Define the "denominator": What is the population at risk of developing disease (i.e., susceptible)?
   - c. Determine whether the observed number of cases clearly exceeds the expected number.
   - d. Calculate the attack rates.
2. Examine the distribution of cases by the following:
   - a. Time
   - b. Place

   } Look for time-place interactions
3. Look for combinations (interactions) of relevant variables
4. Develop hypotheses based on the following:
   - a. Existing knowledge (if any) of the disease
   - b. Analogy to diseases of known etiology
   - c. Findings from investigation of the outbreak
5. Test hypotheses
   - a. Further analyze existing data (case-control studies)
   - b. Refine hypotheses and collect additional data that may be needed.
6. Recommend control measures
   - a. Control of current outbreak
   - b. Prevention of future similar outbreaks
7. Prepare a written report of the investigation and the findings
8. Communicate findings to those involved in policy development and implementation and to the public

investigating an outbreak generally follow this pattern (Box 2.2).

Cross-Tabulation

When confronted with several possible causal agents, as is often the case in a food-borne disease outbreak, a very helpful method for determining which of the possible agents is suspected to be the cause is called *cross-tabulation*. This is illustrated by an outbreak of food-borne streptococcal disease in a Florida jail reported some 50 years ago by the CDC.[23]

In August 1974, an outbreak of group A β-hemolytic streptococcal pharyngitis (sore throat) affected 325 of 690 inmates. On a questionnaire administered to 185 randomly selected inmates, 47% reported a sore throat between August 16 and August 22. Based on a second

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TABLE 2.2 Food-Specific Attack Rates for Items Consumed August 16, 1974, Dade County Jail, Miami

	ATE			DID NOT EAT			
Item Consumed	Sick	Total	% Sick (Attack Rate)	Sick	Total	% Sick (Attack Rate)	*P*
Beverage	179	264	67.8	22	50	44.0	<.010
Egg salad sandwiches	176	226	77.9	27	73	37.0	<.001

From Centers for Disease Control and Prevention. Outbreak of foodborne streptococcal disease. *MMWR*. 1974;23:365.

TABLE 2.3 Cross-Table Analysis for Egg Salad and Beverage Consumed August 16, 1974, Dade County Jail, Miami

	ATE EGG SALAD				DID NOT EAT EGG SALAD			
	Sick	Well	Total	% Sick (Attack Rate)	Sick	Well	Total	% Sick (Attack Rate)
Drank beverage	152	49	201	75.6	19	53	72	26.4
Did not drink beverage	12	3	15	80.0	7	21	28	25.0

From Centers for Disease Control and Prevention. Outbreak of foodborne streptococcal disease. MMWR. 1974;23:365.

questionnaire, food-specific attack rates for items that were served to randomly selected inmates showed an association between two food items and the risk of developing a sore throat: a beverage and an egg salad served at lunch on August 16 (Table 2.2).

In Table 2.2, for each of the suspected exposures (beverage and egg salad), the attack rate was calculated for those who ate or drank the item (were exposed) and those who did not eat or drink the item (were not exposed). For both the beverage and the egg salad, attack rates are clearly higher among those who ate or drank the item than among those who did not. However, this table does not permit us to determine whether the beverage or the egg salad accounted for the outbreak.

In order to answer this question, we use the technique of cross-tabulation. In Table 2.3, we again examine the attack rates in those who ate egg salad compared with those who did not, but this time we look separately at those who drank the beverage and those who did not.

Looking at the data by columns, we see that both among those who ate egg salad and among those who did not, drinking the beverage did not increase the incidence of streptococcal illness (75.6% vs. 80% and 26.4% vs. 25%, respectively). However, looking at the data in the table rows, we see that eating the egg salad increased the attack rate of the illness, both in those who drank the beverage (75.6% vs. 26.4%) and in those who did not (80% vs. 25%). Thus, the egg salad is clearly implicated as the source of the infections. Further discussion of the analysis and interpretation of cross-tabulation can be found in Chapter 15.

This example demonstrates the use of cross-tabulation in a food-borne outbreak of an infectious disease, but the method has broad applicability to any condition in which multiple etiologic factors are suspected. It is discussed further in Chapter 15.

Sometimes multiple agents are responsible for an outbreak. An example is a cruise-ship outbreak of gastrointestinal illness that occurred on the same day as a rainstorm, resulting in billions of liters of storm runoff being contaminated with sewage that had been released on the lake where the cruise took place. The cross-tabulation showed that passengers consuming ice had an attack rate more than twice as high as the rate among those who did not consume ice. Stool specimens were positive for multiple agents, including *Shigella sonnei* and *Giardia*.[24]

CONCLUSION

This chapter reviewed some basic concepts that underlie the epidemiologic approach to acute communicable diseases. Many of these concepts apply equally well to noncommunicable diseases that currently do not

appear to be primarily infectious in origin. Moreover, for an increasing number of chronic diseases originally thought to be noninfectious, infection seems to play some role. Thus, hepatitis B infection is a major cause of primary liver cancer. Papillomaviruses and *Helicobacter pylori* infections are necessary for the development of cervical and gastric cancers, respectively. Epstein-Barr virus has been implicated in Hodgkin disease. The boundary between the epidemiology of infectious and noninfectious diseases has blurred in many areas. In addition, even for diseases that are not infectious in origin, inflammation may be involved, the patterns of spread share many of the same dynamics, and the methodologic issues in studying them are similar. Many of these issues are discussed in detail in Section II.

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REVIEW QUESTIONS FOR CHAPTER 2

1. *Endemic means that a disease:*
   - **a.** Occurs clearly in excess of normal expectancy
   - **b.** Is habitually present in human populations
   - **c.** Affects a large number of countries simultaneously
   - **d.** Exhibits a seasonal pattern
   - **e.** Is prevalent among animals

Questions 2 and 3 are based on the information given below:

The first table shows the total number of persons who ate each of two specified food items that were possibly infective with group A streptococci. The second table shows the number of sick persons (with acute sore throat) who ate each of the various specified combinations of the food items.

Total Number of Persons Who Ate Each Specified Combination of Food Items

	Ate Tuna	Did Not Eat Tuna
Ate egg salad	75	100
Did not eat egg salad	200	50

Total Number of Persons Who Ate Each Specified Combination of Food Items and Who Later Became Sick (With Acute Sore Throats)

	Ate Tuna	Did Not Eat Tuna
Ate egg salad	60	75
Did not eat egg salad	70	15

2. *What is the sore throat attack rate in persons who ate both egg salad and tuna?*
   - **a.** 60/75
   - **b.** 70/200
   - **c.** 60/135
   - **d.** 60/275
   - **e.** None of the above
3. *According to the results shown in the preceding tables, which of the following food items (or combination of food items) is most likely to be infective?*
   - **a.** Tuna only
   - **b.** Egg salad only
   - **c.** Neither tuna nor egg salad
   - **d.** Both tuna and egg salad
   - **e.** Cannot be calculated from the data given
4. *In the study of an outbreak of an infectious disease, plotting an epidemic curve is useful because:*
   - **a.** It helps to determine what type of outbreak (e.g., single-source, person-to-person) has occurred
   - **b.** It shows whether herd immunity has occurred
   - **c.** It helps to determine the median incubation period
   - **d.** *a* and *c*
   - **e.** *a*, *b*, and *c*
5. *Which of the following is characteristic of a single-exposure, common-vehicle outbreak?*
   - **a.** Frequent secondary cases
   - **b.** Increasing severity with increasing age
   - **c.** Explosive
   - **d.** Cases include both people who have been exposed and those who were not exposed
   - **e.** All of the above
6. *Which of the following recent widespread diseases is considered pandemic?*
   - **a.** Ebola virus disease
   - **b.** Middle East respiratory syndrome coronavirus (MERS-CoV)
   - **c.** H1N1 flu virus (swine flu)
   - **d.** Measles

3

The Occurrence of Disease: I. Disease Surveillance and Measures of Morbidity

We owe all the great advances in knowledge to those who endeavor to find out how much there is of anything.
—James Maxwell, physicist (1831–79)

If you can measure that of which you speak, and can express it by a number, you know something of your subject, but if you cannot measure it, your knowledge is meager and unsatisfactory.
—William Thomson, Lord Kelvin, engineer, mathematician, and physicist (1824–1907)

LEARNING OBJECTIVES

- To describe the important role of epidemiology in disease surveillance.
- To compare different measures of morbidity, including incidence rates, cumulative incidence, attack rates, prevalence, and person-time at risk.
- To illustrate why incidence data are necessary for measuring risk.
- To discuss the interrelationship between incidence and prevalence.
- To describe limitations in defining the numerators and denominators of incidence and prevalence measurements.

In Chapter 2, we discussed how diseases are transmitted. It is clear from that discussion that to examine the transmission of disease in human populations, we need to be able to measure the frequency of both disease occurrence and deaths from that disease. In this chapter, we describe disease surveillance in human populations and its importance in providing information about morbidity from disease. We will then discuss how we use rates and proportions to express the extent of morbidity resulting from a disease, and in Chapter 4 we will turn to expressing the extent of mortality in quantitative terms.

SURVEILLANCE

Surveillance is a fundamental role of public health. The Centers for Disease Control and Prevention (CDC) defined epidemiologic surveillance as the "*ongoing systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice closely integrated with the timely dissemination of these data to those who need to know.*"[1] Surveillance may be carried out to monitor changes in disease frequency or to monitor changes in the levels of risks for specific diseases. Much of our information about morbidity and mortality from disease comes from programs of systematic disease surveillance with established infrastructure. Surveillance was commonly conducted for infectious diseases, but in recent years it has become increasingly important in monitoring changes in other types of conditions such as genetic traits, noncommunicable diseases and their risk factors, and environmental toxins, and for injuries and illnesses after natural disasters

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such as hurricanes or earthquakes. In the United States this evidence is commonly generated from the National Health, Nutrition, and Examination Surveys. It is the primary method through which federal agencies in the United States, such as the Environmental Protection Agency (EPA), identify contaminants of emerging concern (CEC). Surveillance is also used to monitor for completeness of vaccination coverage (e.g., COVID-19) and protection of a population and for the prevalence of drug-resistant organisms such as drug-resistant tuberculosis (TB) and malaria.

An important element of this and other definitions of surveillance is providing policy makers with guidance for developing and implementing the best strategies for programs for disease prevention and control. To enable countries or states to develop coordinated public health approaches, mechanisms for information exchange are essential. Consequently, standardized case definitions of disease and diagnostic criteria are needed that can be applied in different countries or for the purpose of public health surveillance within a country. The CDC defines the surveillance case definition as "*a set of uniform criteria used to define a disease for public health*" that is intended to aid public health officials in recording and reporting cases.[2] This is different from a clinical definition that is used by clinicians to make a clinical diagnosis to initiate treatment and meet individual patients' needs. Whether the case definition is used for surveillance purposes or clinical management, the forms used for collecting and reporting data on different diseases must be standardized and clearly defined.

Passive and Active Surveillance

Passive surveillance denotes surveillance in which available data on reportable diseases are used, or in which disease reporting is mandated or requested by the government or the local health authority, with the responsibility for the reporting often falling on the health care provider or district health officer. This type of reporting is also called *passive reporting*. The completeness and quality of the data reported thus largely depend on this individual and their staff, who often take on this role without additional funds or resources. As a result, underreporting and lack of completeness of reporting are likely; to minimize this problem, reporting instruments must be simple and brief so that it does not add additional administrative burden to the already busy health care provider. Examples of reportable diseases include common sexually transmitted infections (syphilis, gonorrhea, human immunodeficiency virus/acquired immune deficiency syndrome [HIV/AIDS]). When passive reporting is used, local outbreaks may be missed because the relatively small number of cases often ascertained is diluted within a large denominator of a total population of a province or country. However, a passive reporting system is relatively inexpensive and relatively easy to develop initially. Monitoring flu outbreaks by assessing internet searches or social media are examples of how this may take place in communities. In addition, as many countries have systems of passive reporting for a number of reportable diseases that are generally infectious, passive reporting allows for international comparisons that can identify areas that urgently need assistance in confirming new cases and in providing appropriate interventions for control and treatment.

Active surveillance denotes a system in which project staff are specifically recruited to carry out a surveillance program that is especially designed for a particular disease, or a set of diseases. They are recruited to make periodic field visits to health care facilities such as clinics, primary health care centers, and hospitals, and to identify new cases of a disease or diseases or deaths from the disease that have occurred (*case finding*). Active surveillance may involve interviewing physicians and patients, reviewing medical records, and, in developing countries and rural areas, surveying villages and towns to detect cases either periodically on a routine basis (e.g., for malaria infection) or after an index case has been reported (e.g., a newly identified case of COVID-19 infection). Reporting is generally more accurate when surveillance is active than when it is passive because active surveillance is conducted by individuals who have been specifically employed and trained to carry out this responsibility.

When passive surveillance is used, existing staff members (commonly physicians) are often asked to report new cases. However, they are often overburdened by their primary responsibilities of providing health care and administering health services. For them, filing reports of new cases is an additional burden that they often view as peripheral to their main responsibilities. Furthermore, with active reporting, local outbreaks are generally more easily identified. But active reporting is more difficult to develop initially and more expensive to set up and maintain than passive reporting.

Surveillance in developing countries may present additional problems. For example, areas in need of surveillance may be physically difficult to reach, and it may be challenging to maintain communication from such areas to the central authorities who must make policy decisions and allocate the resources necessary for follow-up and disease control and prevention activities. Furthermore, definitions of disease used in developed countries may at times be inappropriate or unusable in low- and middle-income countries because of a lack of a functioning laboratory and other sophisticated resources needed for full diagnostic evaluation of suspected cases. The result may therefore be an underreporting of observed clinical cases.

In cases of disease epidemics, the World Health Organization (WHO) and several developed countries, including the United States, mobilize resources to developing countries to aid local public health officials in case finding and data collection. This was evident in the 2014 West Africa Ebola outbreak and the 2015 Zika virus epidemic in Latin America and the Caribbean.

One example of the challenges in disease surveillance using mortality data is the problem of differing estimates of mortality from malaria, one of the leading causes of death today, especially in low- and middle-income countries. In 2004, there was a worldwide peak in malaria deaths. Since then, deaths due to malaria have decreased substantially, particularly in sub-Saharan Africa. This has been attributed to the successful expansion of vector control activities, such as insecticide-treated bed nets to prevent infection and improved treatment of those already infected. In 2019, the World Health Organization (WHO) estimated the global mortality from malaria was 558,000 deaths,[3] which is about 15% lower than what is estimated by the Institute for Health Metrics and Evaluation (IHME) at 643,000 deaths.[4] This disparity in estimates highlights the difficulties in obtaining reliable data in the absence of a standardized surveillance system, vital registration, and routine diagnostic testing.

Surveillance may also be carried out to assess changes in levels of environmental risk factors for disease. For example, monitoring levels of heavy metals, like lead, and its associated adverse health outcomes may be conducted, particularly after an accident has been reported. A unique example of this is the Flint, Michigan water system contamination by lead in 2014. The water source was switched from the Great Lakes to the Flint River without proper treatment and decontamination. This was declared a public health emergency that drew the attention of state and federal public health organizations. The Flint Registry was established in 2017 and remains in place. In addition to its public health goals, the Flint Registry aims at collecting additional information on lead exposure, short- and long-term adverse health outcomes, that will ultimately "*guide policies and programs that prevent and eliminate lead poisoning*".[5] Such monitoring may give an early warning about a possible rise in rates of disease associated with that environmental agent. Thus, surveillance for changes in either disease rates or levels of environmental risk factors may serve as a measure of the severity of the problem and point to possible directions for mitigating such hazards in the future.

STAGES OF DISEASE IN AN INDIVIDUAL AND IN A POPULATION

Let us now consider the levels of a disease in a population over a period of time and how individuals move from one level of disease to another in the population.

Fig. 3.1 shows the timeline for the development of a disease in an individual. An individual is healthy (i.e., without disease), and at some point, biologic onset of a

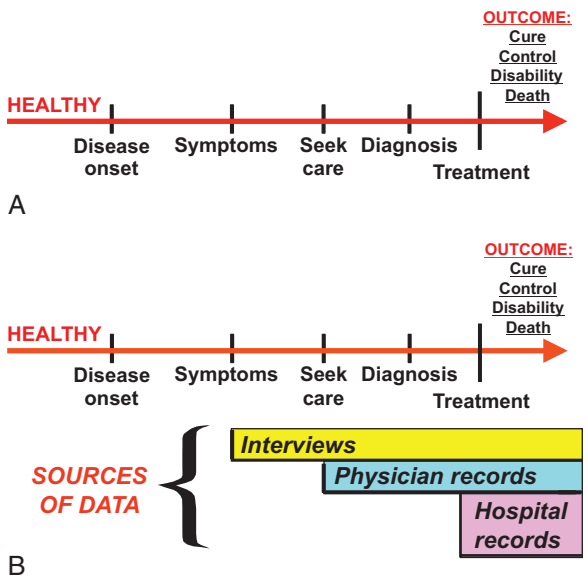

Fig. 3.1 **(A)** The natural history of disease. **(B)** The natural history of disease and some sources of data relating to each interval.

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disease occurs. The person is generally unaware of the point in time when the disease begins. Later, symptoms develop and lead the patient to seek medical attention. In certain situations, hospitalization may be required, either for diagnosis or for treatment, or for both. In any case, at some point a diagnosis is made and treatment may then follow. One of several outcomes can then result: cure, control of the disease, disability, or death. (This will be examined in further detail in Chapter 18 under "Natural History of Disease.")

Fig. 3.2A–D shows the progression of disease in a population as reflected by the levels of illness and medical care. The outside rectangle represents the total population (see Fig. 3.2A), and the smaller rectangle represents the smaller subset of sick people (see Fig. 3.2B). As a person becomes ill, they move within the sick group to those who seek care and to the subset of those who are hospitalized, from the outside rectangle to the progressively smaller rectangles in the diagram as shown by the curved arrows (see Fig. 3.2C). As seen in Fig. 3.2D, deaths occur in all of these rectangles, as shown by the small straight arrows, but the death rate is proportionately greater in groups with more severe illness such as in those who are hospitalized.

Which sources of data can be used to obtain information about the person's illness? For the period of the illness that necessitates hospitalization, medical and hospital records are useful (see Fig. 3.1C). If hospitalization is not required, primary care providers' records may be the best and most reliable source of information. If we want information about the illness before medical care was sought, we may obtain this information from the patient using a questionnaire or an interview. If the patient cannot provide this information, we may obtain it from a family member or someone else who is familiar with the patient's health status. Not shown in this figure are the records of health insurers, which at times can provide very useful information.

The source of data from which cases are identified clearly influences the rates that we calculate for expressing

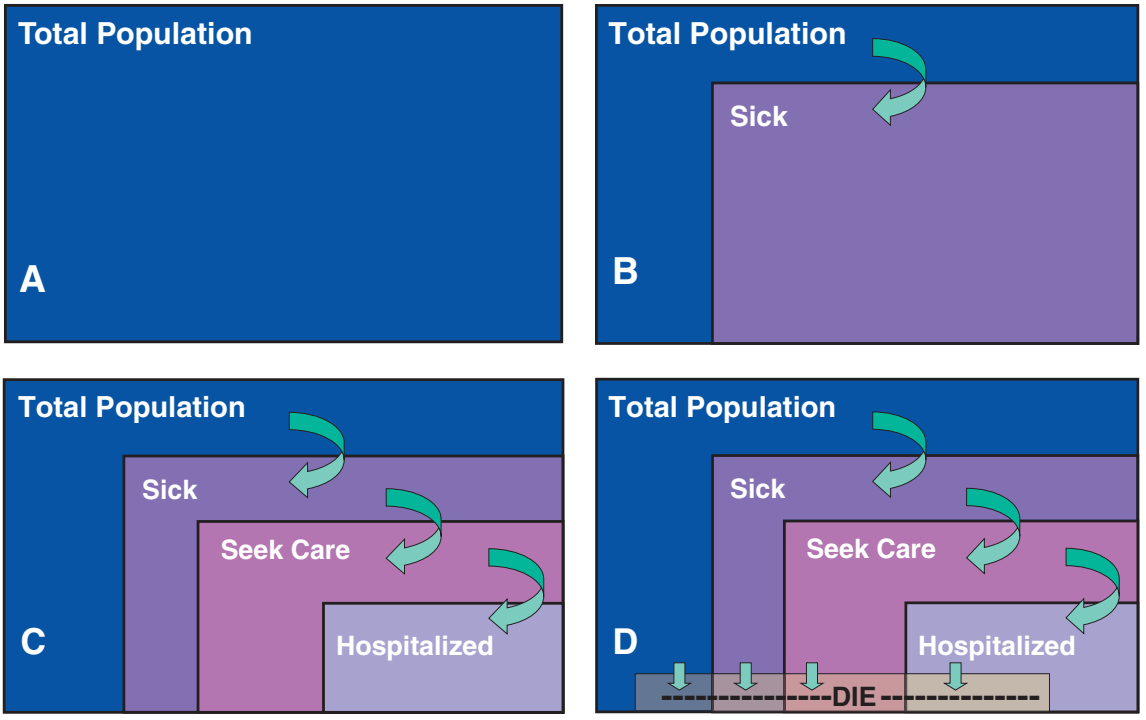

Fig. 3.2 **(A–C)** The population: progression from health to varying degrees of disease severity. **(D)** The population: the occurrence of deaths in each group. (Modified from White KL, Williams TF, Greenberg BG. The ecology of medical care. *N Engl J Med.* 1961;265:885–892.)

the frequency of disease. For example, hospital records will not include data about patients who obtained care only in physicians' offices. Consequently, when we see rates for the frequency of occurrence of a certain disease, we must identify the sources of the cases and determine how the cases were identified. When we interpret these rates and compare them to rates reported in other populations and at other times, we must take into consideration the characteristics of the sources from which the data were obtained.

Occurrence of disease can be measured using rates or proportions. *Rates* express the frequency of a given event (disease case or death) in relation to a unit of time; *proportions*, a subset divided by whole, tell us what fraction of the population has the disease of interest. Let us turn to how we use rates and proportions for expressing the extent of disease in a community or other population. In this chapter, we discuss measures of illness or morbidity; measures of mortality are discussed in Chapter 4.

MEASURES OF MORBIDITY

Incidence

The critical element in defining incidence is *NEW* cases of disease, sometimes called *incident cases*. Incidence is a measure of new events—the disease is identified in a person who newly develops the disease and did not have the disease previously. This can only be observed in longitudinal studies such as cohort studies and clinical trials. Because the incidence is a measure of events (i.e., transition from a nondiseased to a diseased state), it is a measure of risk. This risk can be looked at in any population group, such as a particular age group, among males or females, in an occupational group, or a group that has been exposed to a certain environmental agent, such as radiation or a chemical toxin.[a]

The denominator of the incidence represents the people who are *AT RISK* for developing the disease. For the incidence to be meaningful, any individual who is included in the denominator must have the *potential* to become part of the group that is counted in the numerator. Thus, if we are calculating incidence of uterine cancer, the denominator must include only females with no history of hysterectomy, because females with a history of hysterectomy and males would never have the potential to become part of the group that is counted by the numerator, that is, both are not at risk for developing uterine cancer. Although this example seems obvious, it is not always so clear, and we shall return to this issue later in the discussion.

Another important issue regarding the denominator is the issue of time. Incidence measures can use two types of denominators: people at risk who are observed throughout a defined time period, or units of time when each person is observed (person time). Let us consider each of these approaches.

People at Risk Who Are Observed Throughout a Defined Time Period – *Cumulative Incidence*

In the first type of denominator for incidence, we specify a period of time, and we must know that all of the individuals in the group represented by the denominator have been followed up the maximum period when the individuals remain under observation. This is called *cumulative incidence*. It is defined as the frequency of *new* cases of a disease that occur during a specified period of time in a population *at risk* for developing the disease.

$$\text{Incidence per 1,000} = \frac{\text{No. of new cases of a disease occurring in the population during a specified period of time}}{\text{No. of persons who are at risk of developing the disease during that period of time}} \times 1{,}000$$

The choice of time period is arbitrary: We could calculate incidence in 1 week, incidence in 1 month, incidence in 1 year, incidence in 5 years, and so on. The important point is that whatever time period is used in the calculation must be clearly specified, and all individuals included in the calculation must have been observed, and, of course, at risk of developing the outcome of interest, during follow-up. The incidence is calculated using a period of time during which all of the individuals in the population are considered to be at risk for the outcome, which is itself a measure of risk. Imagine an epidemiologist is investigating cases of food poisoning that occurred among some passengers aboard an airplane on a 10-hour transatlantic flight. Since all

[a]Incidence can be incidence of new cases, recurrent events or deaths. In other words, there are only two general markers of frequency: incidence and prevalence.

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passengers entered the airplane at the same time, exited the plane at the same time, and some experienced symptoms of food poisoning, then all passengers have been followed up for the same amount of time; 10 hours. Thus, in this case, the *cumulative incidence* is an appropriate measure of risk.

The result in the above mentioned equation has been multiplied by 1,000 so that we can express the incidence per 1,000 persons. The choice of 1,000 is more or less arbitrary—we could have used 10,000, 1 million, or any other figure. However, this choice is generally influenced by the frequency of the disease; for example, for a common disease, such as the common cold, incidence is usually defined as a percentage; for rare diseases, such as aplastic anemia, it is multiplied by 100,000 or even 1,000,000.

For example, Fig. 3.3 shows trends in incidence of thyroid cancer in children in Belarus, Ukraine, and Russia from 1986 to 1994, obtained from surveillance data following an explosion in the Chernobyl reactor.[6] The highest incidence rates were found in the most contaminated areas—Gomel in southern Belarus and parts of northern Ukraine. However, a problem in interpreting such data is the possibility that the observed increase could be due to more intensive screening that was initiated following the accident. Such screening could have identified thyroid tumors that might otherwise not have been detected and thus might not have been attributed to the common exposure (the reactor). Nevertheless, there is now general agreement that the observed increase in thyroid cancer in children and adolescents in areas exposed to Chernobyl fallout was, in fact, real.

When All People Are Not Observed for the Full Time Period, Person-Time, or Units of Time When Each Person Is Observed – *Incidence Rate*

Often, every individual in the denominator cannot be followed for the full time specified for a variety of reasons, including loss to follow-up or death from a cause other than that being studied. When different individuals are observed for different lengths of time, as occurs most commonly in longitudinal studies, we can calculate an *incidence rate* (also called an *incidence density*), in which the denominator consists of the sum of the *units of time* that each individual was at risk and was observed. This is called *person-time* and is often expressed in terms of person-months, person-years (py) or, in acute outbreaks, person-weeks or person-days of observation.

Let us consider py: One person at risk who is observed for 1 year = 1 py. One person at risk observed for 5 years = 5 py. But 5 people at risk, each of whom is observed for only 1 year, also yields 5 py.

Let us assume we have a 5-year study and five people have been observed for the entire period (as indicated by the arrow for each person in Fig. 3.4). In each of the 5 years of the study, all five participants are observed, so that we have 5 py of observation in each of the 5 years, for a total of 25 py of observation in the entire study.

Now let us consider the situation where all five people at risk are not observed for the entire 5 years of the study but are observed for different lengths of time

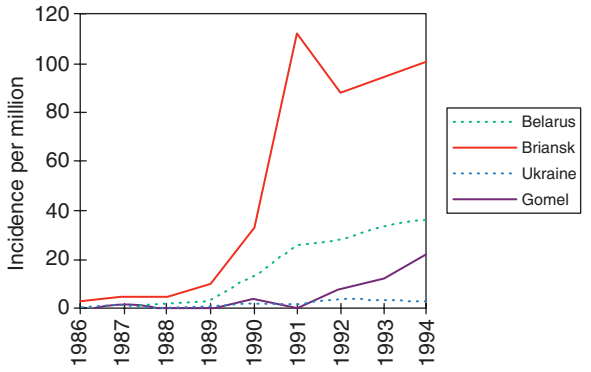

Fig. 3.3 Trends of incidence of childhood thyroid cancer in Belarus, Ukraine, and Russia, 1986–94. (From Bard D, Verger P, Hubert P. Chernobyl, 10 years after: health consequences. *Epidemiol Rev.* 1997;19:187–204.)

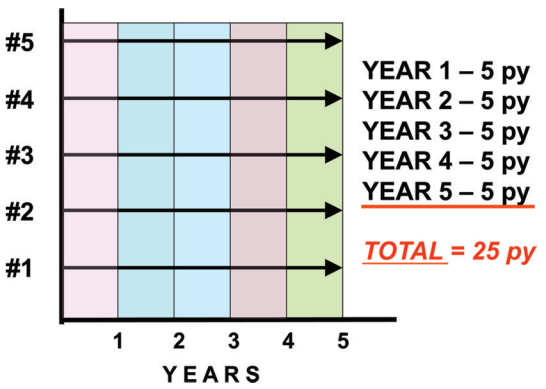

Fig. 3.4 When all the people in the population being studied are observed for the entire period: person-years *(py)* of observation.

(Fig. 3.5A). In this diagram, the two arrows represent two people who were observed for all 5 years. The timelines for the three other people end with a red "x," which indicates the point at which the observation of each individual ended, either because the event of interest occurred or because the person was lost to follow-up ("censored observation"), or other problems.

How do we calculate the total number of py observed in this study? Let us look at the first year of the study (see Fig. 3.5B). All five people were observed during the

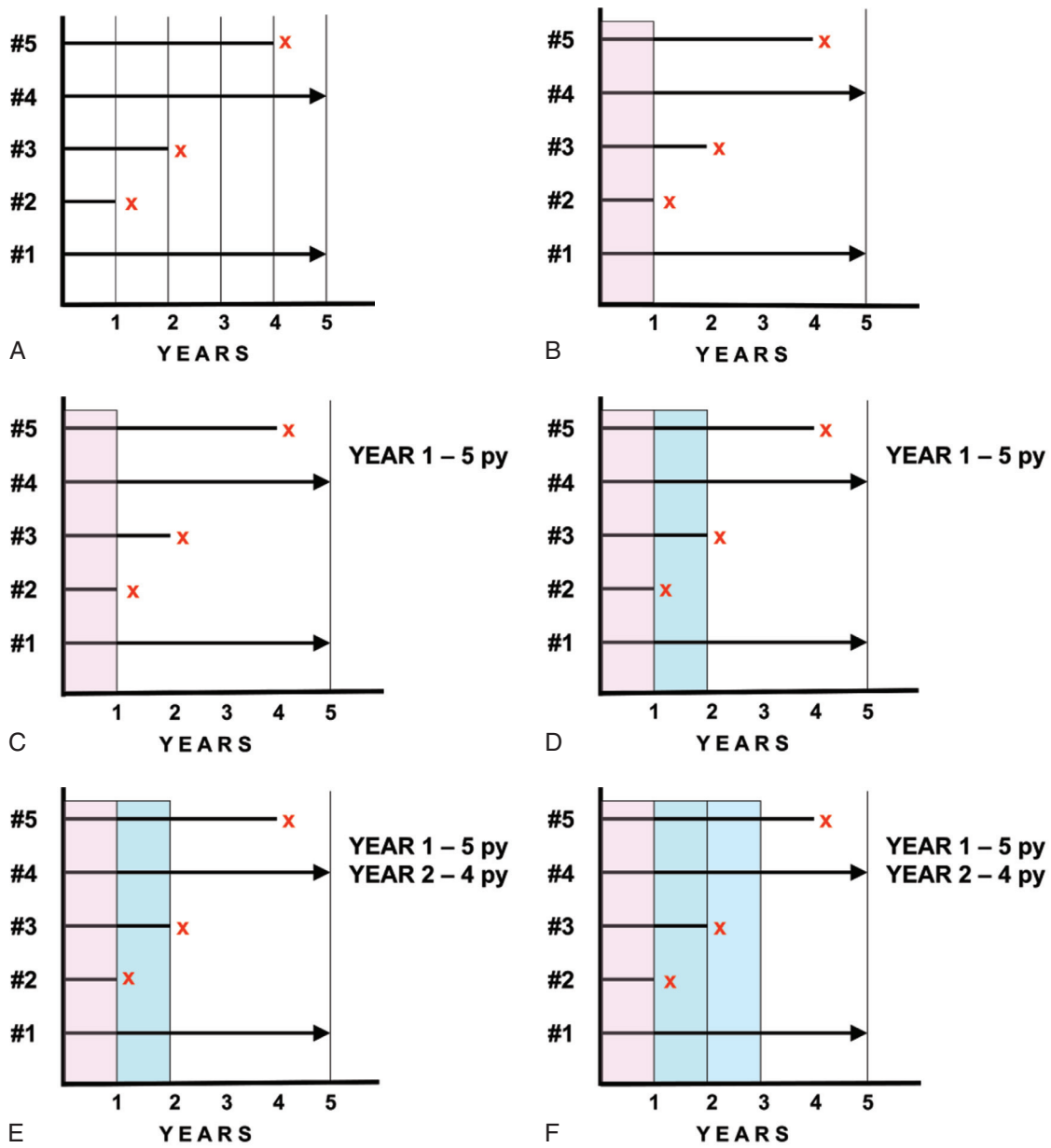

Fig. 3.5 (A–L) But what if the people at risk in the population are observed for different lengths of time? Calculation of person-time as person-years *(py)* observed. (See page 48 for explanation in text.)

Continued

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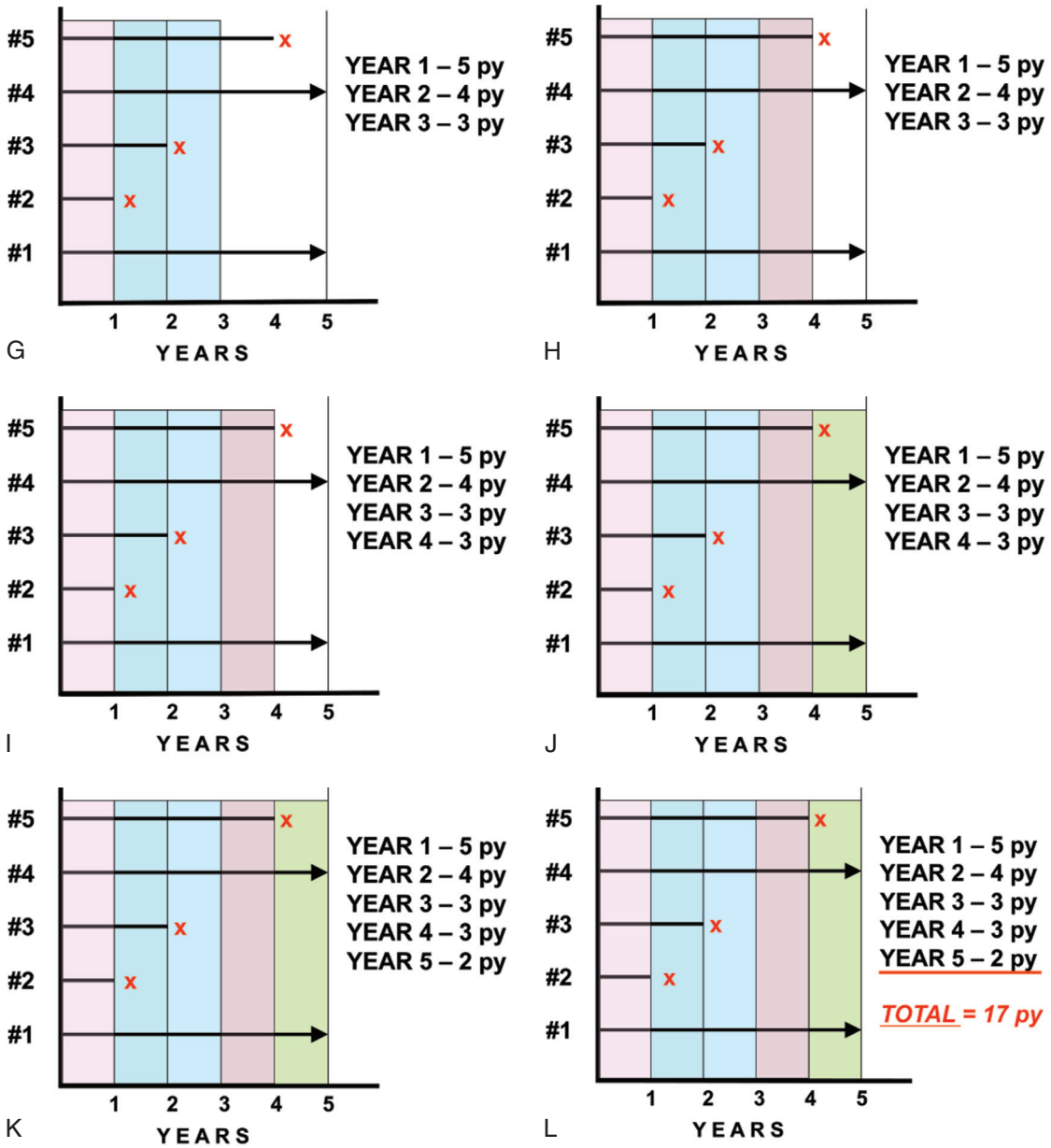

Fig. 3.5, cont'd

first year, so we have 5 py of observation in the first year (see Fig. 3.5C).

Now look at the second year of the study (see Fig. 3.5D). Note that participant No. 2 was only observed for the first year, so that in the second year we have only four participants, each of whom contributed 1 year of follow-up to the study for a total of 4 py (see Fig. 3.5E).

Looking at the third year of the study, we see that participant No. 3 was only observed for the first 2 years of the study (see Fig. 3.5F). Therefore only three participants were observed in the third year, generating 3 py

of observation during the third year (see Fig. 3.5G). These participants were also all observed for the fourth year of the study (see Fig. 3.5H) and they again contributed 3 py of observation during the fourth year of the study (see Fig. 3.5I).

Finally, let us look at the fifth year of the study (see Fig. 3.5J). We see that participant No. 5 was only observed for the first 4 years of the study. As a result, only two participants remained and were observed in the fifth year of the study. They contributed 2 py of observation during the fifth year (see Fig. 3.5K). As seen in Fig. 3.5L, we therefore had 5 + 4 + 3 + 3 + 2 py of observation during the entire 5-year study, yielding a total of 17 py of observation. (This compares with 25 py of observation if all five participants had been observed throughout the entire 5 years of the study, as seen in Fig. 3.4.) Thus, *if people at risk are observed for different periods of time*, the incidence rate is:

$$\text{Incidence rate per 1,000 person} - \text{time} = \frac{\text{Number of NEW cases of a disease occurring in a population during a specified period of time}}{\text{Total person} - \text{time (the sum of the timeperiods of observation of each person who has been observed for all or part of the entire time period)}} \times 1{,}000$$

Person-time is discussed further in Chapter 6.

Identifying NEW Cases in Order to Calculate Incidence

Practically speaking, when we wish to calculate incidence, how do we identify all new cases in a population during a specified time period? In certain situations, it may be possible to monitor an entire population over time with tests that can detect newly developed cases of a disease, or use of population registries. However, often this is not possible and instead a population is identified and screened for the disease at baseline (prevalent cases defined in the next section) (Fig. 3.6). Those who do not have the disease at baseline are followed for the specified time, such as 1 year. They are then rescreened to see if they have developed the disease of interest (Fig. 3.7). Any cases that are identified clearly developed disease during the 1-year period since those followed were free of disease at the beginning of the year. Thus, these cases

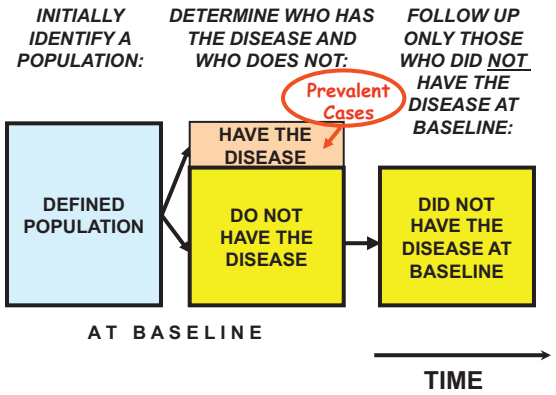

Fig. 3.6 Identifying newly detected cases of a disease. Step 1: screening for prevalent cases at baseline.

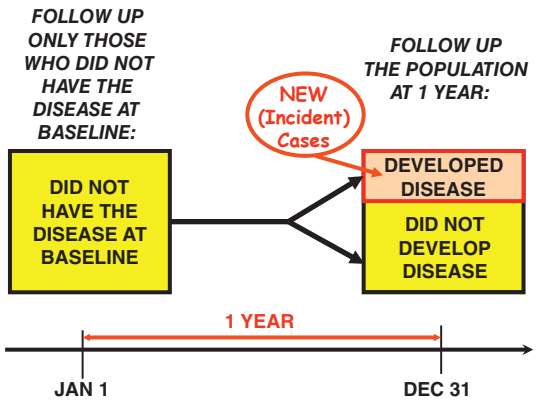

Fig. 3.7 Identifying newly detected cases of a disease. Step 2: follow-up and rescreening at 1 year to identify cases that developed during the year.

are new or incident cases and serve as the numerator for the incidence rate.

Although in most situations it is necessary to express incidence by specifying a denominator, at times, the number of cases alone may be informative. For example, Fig. 3.8 shows the number of reported TB cases, United States, 1953–2020. The number of cases reported in a year in the United States (since reporting began) reached an all-time low in 2015. Despite a plateau from 1980 to 1985, the reported number of cases of TB increased by approximately 20% between 1985 and 1992. Much of the increase in TB seen here was associated with the rapidly expanding identification of infections with

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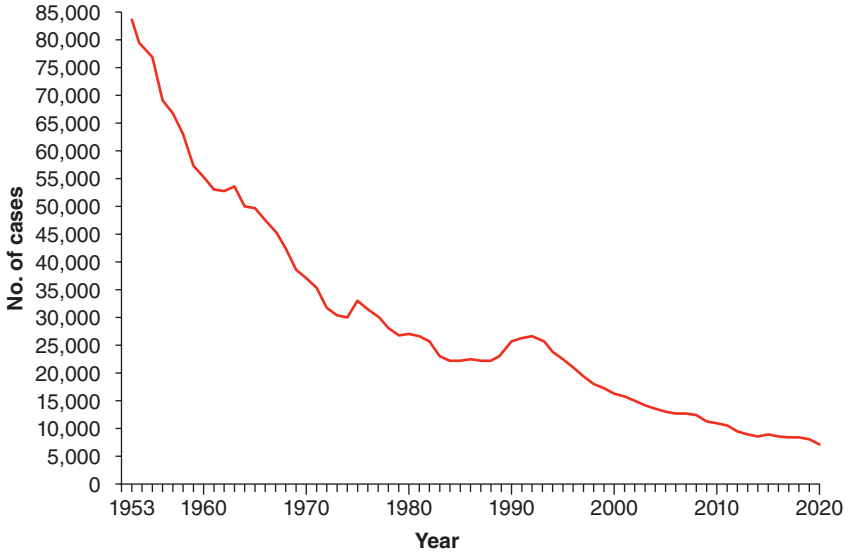

Fig. 3.8 Reported tuberculosis cases, United States, 1953–2020 (as of Oct 5, 2021). (From Centers for Disease Control and Prevention [CDC]. *TB Incidence in the United States, 1953-2020*. Atlanta, GA: US Department of Health and Human Services, CDC; 2021 https://www.cdc.gov/tb/statistics/tbcases.htm.

HIV. However, even before AIDS and HIV were recognized as major public health problems, TB had remained a serious, but often neglected problem, particularly in certain urban areas of the United States. From 1992 until 2008, the total number of TB cases decreased 2% to 7% annually. This is an example in which a graph that just plots numbers of cases without a denominator can be very helpful when there is no reason to suspect a significant change in the denominator during a given time period.

In general, however, our goal in calculating incidence is to be able to do so with the information needed for both the numerator and denominator so that valid comparisons can be made. Fig. 3.9 presents trends in incidence rates for selected cancers by sex in the United States for males *(left)* and females *(right)* from 1975 to 2018. As seen there, lung cancer incidence has been declining in males and leveling off in females. After marked rises in incidence for many years, prostate cancer in men has been declining since 2001. Breast cancer in females in the United States declined between 1998 and 2003, followed by a slight increase from 2004 to 2013. After having been level for a number of years, colon and rectal cancers have been decreasing in both sexes.

Attack Rate

Occasionally, time associated with the denominator may be specified implicitly rather than explicitly. For example, in Chapter 2 we discussed investigating a food-borne disease outbreak, in which we speak of an *attack rate*, which is defined as the number of people exposed to a suspect food who became ill, divided by the number of people who were exposed to that food. The attack rate does not explicitly specify the time interval because for many food-borne disease outbreaks we know that most cases occur within a few hours up to a few days after the exposure. Consequently, cases that develop months later are not considered part of the same common-source outbreak. However, in many situations, current knowledge of the biology and natural history of the disease does not clearly define a time frame, and so the time must be stated explicitly. A further consideration is that attack rate is not truly a rate but a proportion. Since the term *rate* should include a time unit in the calculation, a food-borne *attack rate* is not an accurate term because it actually tells us the *proportion* of all people who ate a certain food who became ill. In essence, *attack rate* is a *cumulative incidence* as explained earlier in this chapter. However, the term *attack rate* has been traditionally used in epidemiologic

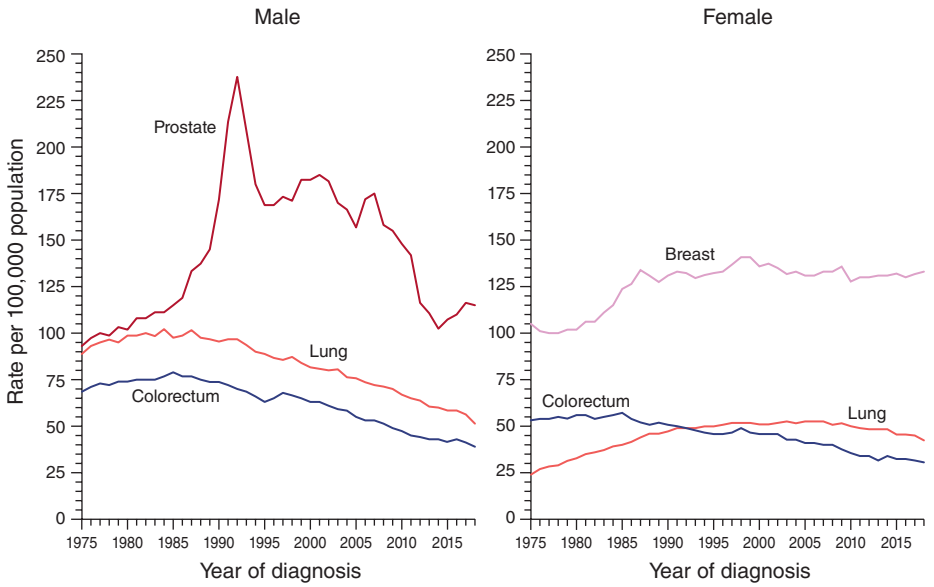

Fig. 3.9 Annual age-adjusted cancer incidence rates among males and females for selected cancers, United States, 1975–2019 (age-adjusted to the 2000 US standard population). (Modified from Siegel R, Miller K, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67:7–30. Data from National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Statistics Explorer Network. SEER Explorer Application: https://seer.cancer.gov/statistics-network/)

investigations for a long time. We will go on to discuss the use of proportions in measuring the occurrence of disease below.

Prevalence

Prevalence proportion is defined as the number of affected persons present in the population at a specific time divided by the number of persons in the population at that time; that is, what proportion of the population is affected by the disease at that time? While prevalence may be mistakenly referred to as the *prevalence rate* in the medical literature, this is inaccurate since it is a proportion.

$$\text{Prevalence per } 1{,}000 = \frac{\text{No. of cases of a disease present in the population at a specified time}}{\text{No. of persons in the population at that specified time}} \times 1{,}000$$

For example, if we are interested in knowing the prevalence of arthritis in a certain community on a certain date, we might visit every household in that community and, using interviews or physical examinations, determine how many people have arthritis on that day. This number becomes the numerator for prevalence. The denominator is the population in the community on that date.

What is the difference between *incidence* and *prevalence*? Prevalence can be viewed as a snapshot or a slice through the population at a point in time at which we determine who has the disease and who does not. But in so doing, we are not determining when the disease developed. Some individuals may have developed arthritis yesterday, some last week, some last year, and some 10 or 20 years ago. Thus, when we survey a community to estimate the prevalence of a disease, we generally do not take into account the duration of the disease. Consequently, the numerator of prevalence includes a mix of people with different durations of disease, and as a result we do not have a measure of risk. If we wish to measure risk, we must use incidence, because in contrast to prevalence, it includes only new cases or events and a specified time period during which those events occurred.

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TABLE 3.1 Examples of Point and Period Prevalence and Cumulative Incidence in Interview Studies of Asthma

Interview Question	Type of Measure
"Do you currently have asthma?"	Point prevalence
"Have you had asthma during the last [*n*] years?"	Period prevalence
"Have you ever had asthma?"	Cumulative incidence

In the medical and public health literature, the word *prevalence* is often used in two ways:

- *Point prevalence:* Prevalence of the disease at a certain point in time—this is the use of the term *prevalence* that we have just discussed.
- *Period prevalence:* How many people have had the disease at any point during a certain time period? The time period referred to may be arbitrarily selected, such as a month, a single calendar year, or a 5-year period. Some people may have developed the disease during that period, and others may have had the disease before and died or been cured during that period. The important point is that every person represented by the numerator had the disease at some time during the period specified.

The two types of prevalence, as well as cumulative incidence, are illustrated in Table 3.1 using questions regarding asthma.

Returning to *point prevalence*, practically speaking, it is virtually impossible to survey an entire city on a single day. Therefore although conceptually we are thinking in terms of a single point in time, in reality, the survey would take much longer (e.g., weeks or months). When we just see the word *prevalence* used without any modifier, it generally refers to point prevalence, and for the rest of this chapter, we will use *prevalence* to mean point prevalence.

Let us consider incidence and prevalence. Fig. 3.10 shows five cases of a disease in a community in 2020. The first case of the disease occurred in 2019, and the patient died in 2020.

The second case developed in 2020 and continued into 2021. The third case was a person who became ill in 2020 and was cured in 2020. The fourth case occurred in 2019, and the patient was cured in 2020. The fifth case occurred in 2019 and continued through 2020 and into 2021.

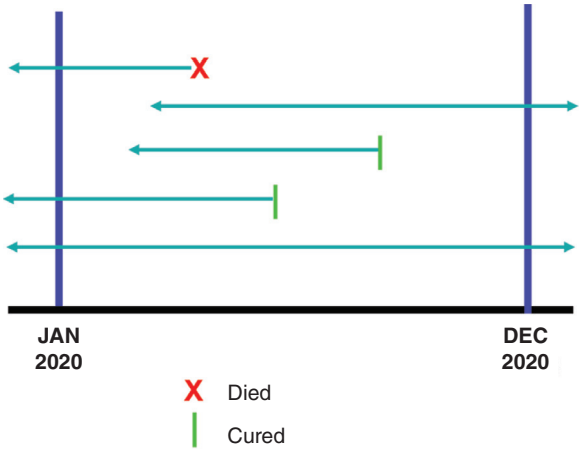

Fig. 3.10 Example of incidence and prevalence: I.

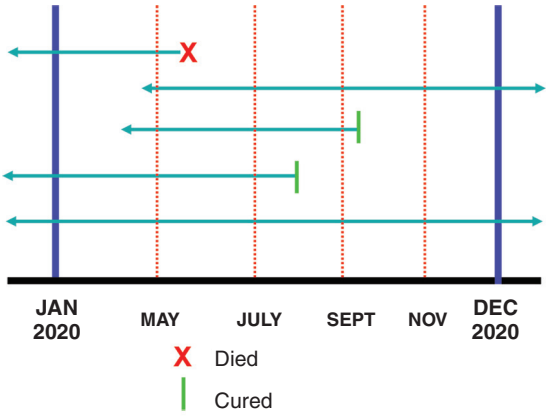

Fig. 3.11 Example of incidence and prevalence: II.

For this example, we will consider only the cases (numerators) and will ignore the denominators. In this example, what is the numerator for incidence in 2020? We know that incidence counts only new cases, and because two of the five cases developed in 2020, the numerator for incidence in 2020 is 2.

What about the numerator for point prevalence in 2020? This depends on when we do our prevalence survey (Fig. 3.11). If we do the survey in May, the numerator will be 5. If we do the survey in July, the numerator will be 4. If we do the survey in September, however, the numerator will be 3, and if we do it in December, the numerator will be 2. Thus, the prevalence will depend on specifically when during the year the survey is performed.

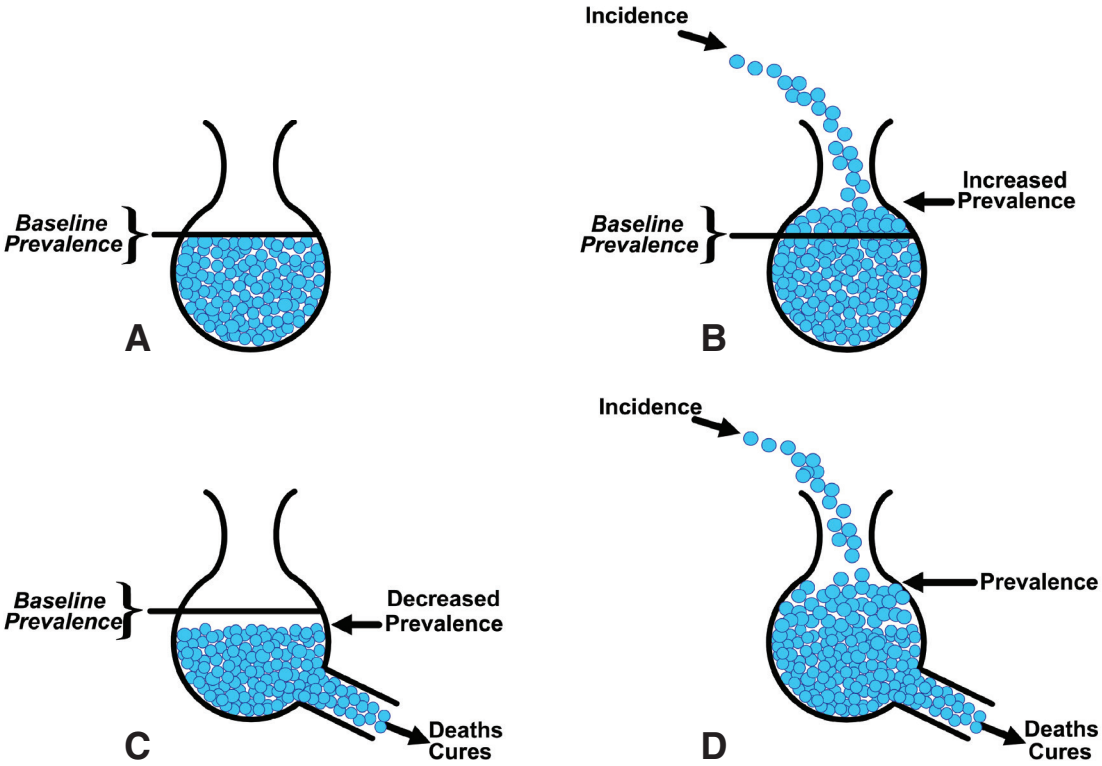

Fig. 3.12 Relationship between incidence and prevalence. **(A)** Level of prevalence in the population. **(B)** Increased prevalence resulting from incidence. **(C)** Decreased prevalence resulting from deaths and/or cures. **(D)** Overall impact on prevalence of incidence, deaths, and/or cures.

Fig. 3.12A–D shows the dynamic relationship between incidence and prevalence. A flask is shown that represents a community (see Fig. 3.12A), and the beads in the flask represent the prevalent cases of a disease in the community. How can we add to or increase the *prevalence*? As seen in Fig. 3.12B, we can do so through *incidence*—by the addition of new cases. What if we could drain beads from the flask and lower the prevalence? How might this be accomplished? As seen in Fig. 3.12C, it could occur through either death or cure. Clearly, these two outcomes represent a major difference to a patient, but with regard to prevalence, cure and death have the same effect: they reduce the number of diseased persons in the population and thus lower prevalence. Therefore, what exists is the dynamic situation shown in Fig. 3.12D. A continual addition of new cases (incidence) increases the prevalence, while death and/or cure decrease the prevalence.

This effect of lowering prevalence through either death or cure underlies an important issue in public health and clinical medicine. For example, when insulin first became available, what happened to the prevalence of diabetes? The prevalence increased because diabetes was not cured but was only controlled. Many patients with diabetes who formerly would have died now survived; therefore, the prevalence increased. This seeming paradox is often the case with public health programs: a new health care intervention (e.g., highly active antiretroviral therapy for HIV infection) is introduced that enhances survival (fewer then die of HIV/AIDS) or it may work by early detection of disease in more people, and the net effect is an apparent increase in prevalence. It may be difficult to convince some people that a program is successful if the prevalence of the disease that is the target of the program actually increases. However, this clearly occurs when death is prevented, and the

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disease is not cured or eradicated although it may be well controlled.

We have said that prevalence is not a measure of risk. If so, why bother to estimate prevalence? Prevalence is an important and useful measure of the burden of disease in a community to inform resource allocation by decision-makers. For example, how many people in the community have osteoarthritis? This information might help us to determine, for example, how many clinics are needed, what types of rehabilitation services are needed, and how many and which types of health professionals are needed. Prevalence is therefore valuable for planning health services. When we use prevalence, we also want to make future projections and anticipate the changes that are likely to take place in the disease burden. However, if we want to look at the cause, or etiology, of disease, we must explore the relationship between an exposure and the risk of disease, and to do this, we need data on incidence.

Nevertheless, prevalence data may at times be very useful—they may be suggestive if not confirmatory in studies of the etiology of certain diseases. For example, asthma is a disease of children for which incidence is difficult to measure because the exact time of the beginning of the disease (its inception) is often hard to determine, given the difficulties in defining the disease and ascertaining the initial symptoms. For this reason, when we are interested in time trends and geographic distribution of asthma, prevalence is the measure most frequently used. Information on prevalence of asthma is often obtained from self-reports such as interviews or questionnaires.

Fig. 3.13 shows the adjusted prevalence of stages 3 and 4 chronic kidney disease (CKD) in US adults, by presence or absence of diabetes, from the National Health and Nutrition Examination Survey (NHANES) 1988–94 through 2011–12; NHANES conducts yearly cross-sectional studies with samples that are representative of the US general population. CKD was defined as an estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m^2, estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from calibrated single serum creatinine measurements. We can observe an initial increase in adjusted prevalence of stages 3 and 4 CKD, which stopped around the 2000s among nondiabetic individuals, whereas the prevalence continued to increase for diabetic individuals.

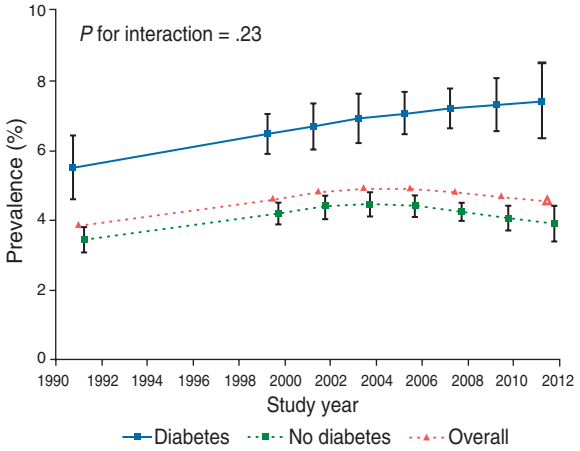

Fig. 3.13 Adjusted prevalence of stages 3 and 4 chronic kidney disease (estimated glomerular filtration rate of 15 to 59 mL/min/1.73 m^2 calculated with Chronic Kidney Disease Epidemiology Collaboration equation) in US adults, by age, 1990–2012. (From Murphy D, McCulloch CE, Lin F, et al. Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med.* 2016;165:473–481.)

This could be partly explained by the longer survival of diabetic CKD patients.

Another example of the value of prevalence data is seen in Fig. 3.14. One of the most significant and challenging public health problems today in the United States and in other high-income developed countries is the dramatically increasing prevalence of obesity. Obesity is associated with significant morbidity and mortality and is a risk factor for diseases such as arthritis, hypertension, type 2 diabetes, coronary disease, and stroke. In this figure, in which self-reported prevalence of obesity by state is shown for 2020, no state reported a prevalence of obesity of less than 24%, and 33 had a prevalence equal to or greater than 30%. We can also observe that the highest prevalence of obesity is in the Southern states.

One limitation of these data is that they are based on self-reported heights and weights given by respondents by telephone. Survey respondents, especially in telephone surveys of obesity, generally understate their weights, overstate their heights, or both. In this study, the participants were classified according to their body mass index (BMI), which is defined as a person's weight in kilograms divided by the square of the person's height in meters (BMI = weight [kg]/height^2 [meters^2]). A BMI of

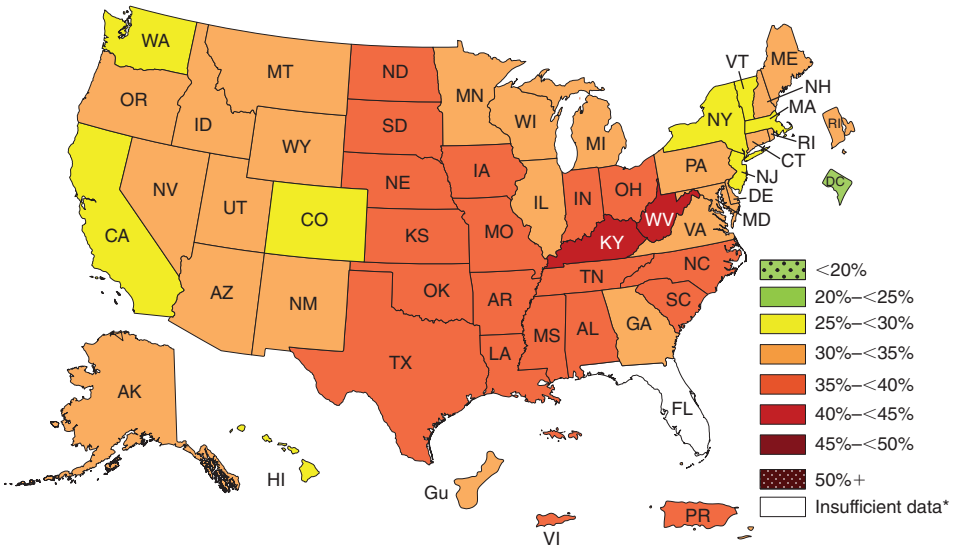

Fig. 3.14 Prevalence of self-reported obesity among US adults by state and territory, Behavioral Risk Factor Surveillance System, 2020. (Modified from Centers for Disease Control and Prevention. https://www.cdc.gov/obesity/data/maps/2021/overall-obesity-prevalence-map-2011-2021-508.pdf)

BOX 3.1 Some Sources of Morbidity Statistics

1. Disease reporting—communicable diseases, cancer registries
2. Data accumulated as a by-product of insurance and prepaid medical care plans
   a. Group health and accident insurance
   b. Prepaid medical care plans
   c. State disability insurance plans
   d. Life insurance companies
   e. Hospital insurance plans—Blue Cross
   f. Railroad Retirement Board
3. Tax-financed public assistance and medical care plans
   a. Public assistance, aid to the blind, aid to the disabled
   b. State or federal medical care plans
4. Hospitals and clinics
5. Absenteeism records—industry and schools
6. Pre-employment and periodic physical examinations in industry and schools
7. Case-finding programs
8. Records of military personnel
   a. Armed Forces
   b. Veterans Administration
9. Morbidity surveys on population samples (e.g., National Health Survey, National Cancer Surveys)

25–29 is categorized as *overweight* and a BMI of 30 or greater as *obese*. The result is likely an underestimation of obesity prevalence based on BMI so that the true prevalence of obesity by state is probably higher than that seen in Fig. 3.14. Given the trends described above and seen in Fig. 3.14, an enormous public health effort and commitment will be needed to reverse this steadily worsening public health problem. In addition, the use of BMI itself to define obesity has its own limitations. BMI does not distinguish between excess fat, muscle, or bone mass, and does not provide any information on the fat distribution within each individual.

Box 3.1 lists some possible sources of morbidity statistics. Each has its limitations, primarily because most of these sources are not established for research purposes but rather for administrative or billing purposes. Therefore, they may be characterized by incomplete or ambiguous data and, at times, may only refer to a highly selected population that may not be representative of the population to which we would like to generalize the findings.

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TABLE 3.2 Definitions 1–5 of Health Care–Associated *Staphylococcus aureus* Bacteremia

Highest level of stringency	Definition	Criteria: Blood culture performed within 2 days of admission and the following:
	1.	• Any hospital inpatient admission within the previous 30 days
	2.	• Any hospital inpatient admission within the previous 30 days or • Hospital outpatient clinic contact including surgery or contact to clinics of oncology, hematology, or nephrology within the previous 30 days
Lowest level of stringency	3.	• Any hospital inpatient admission within the previous 30 days or • Any type of hospital outpatient clinic contact within the previous 30 days
	4.	• Any hospital inpatient admission within the past 90 days or • Any type of hospital outpatient clinic contact within the previous 30 days
	5.	• Any hospital inpatient admission within the past 90 days or • Any type of hospital outpatient clinic contact within the previous 30 days or • Antibiotic or immunosuppressive therapy 30 days prior to admission

Modified from Smit J, Søgaard M, Schønheyder HC, et al. Classification of healthcare-associated *Staphylococcus aureus* bacteremia: influence of different definitions on prevalence, patient characteristics, and outcome. *Infect Control Hosp Epidemiol.* 2016;37(2): 208–211.

Problems With Incidence and Prevalence Measurements

Problems With Numerators

The first problem is defining who has the disease. Some diseases are difficult to diagnose, and when such a diagnostic difficulty arises, expert groups are often convened to develop sets of diagnostic criteria. There are five sets of diagnostic criteria for health care–associated (HCA) *Staphylococcus aureus* bacteremia, each with different level of stringency (Table 3.2). Fig. 3.15 shows the proportion of patients classified as having HCA *S. aureus* bacteremia (SAB) according to the five different definitions in 2,638 patients using data from Northern Denmark in between 2000 and 2011. We see that the prevalence estimate is significantly affected by the set of criteria that is used.

Another example is given by a cohort of 1,879 men and women 65 years of age and older who were enrolled in the Canadian Study of Health and Aging (CSHA) and followed up over a ten-year period from 1991 to 2001.[7] The proportion who were given a diagnosis of dementia using six commonly used classification systems was calculated. Depending on which diagnostic system was used, the proportion of subjects with dementia varied from 3.1% to 29.1% (Fig. 3.16). This marked variation in prevalence estimates has important potential implications both for research and for the provision of appropriate health services. When the results of any morbidity survey are reported, it is essential that the precise definition used for a case be clearly specified. The decision as to which definition to use is not always simple. Often it will largely depend on the specific purpose for which a given survey has been conducted.

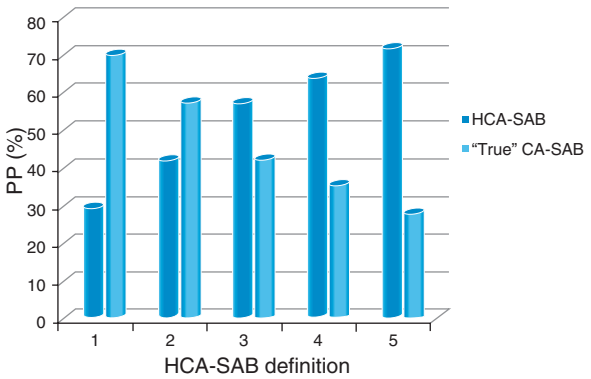

Fig. 3.15 Prevalence proportion *(PP)* of patients classified as health care–associated *Staphylococcus aureus* bacteremia *(HCA-SAB)* and true community-acquired *(CA)* SAB according to the five different definitions. (Modified from Smit J, Søgaard M, Schønheyder HC, et al. Classification of healthcare-associated *Staphylococcus aureus* bacteremia: influence of different definitions on prevalence, patient characteristics, and outcome. *Infect Control Hosp Epidemiol.* 2016;37:208–211.)

The next issue relating to numerators is that of ascertaining which persons should be included in the numerator. How do we find the cases? We can use regularly available data or, as discussed earlier in this chapter (passive *versus* active surveillance), we can conduct a study specifically designed to gather data for estimating incidence or prevalence. In many such studies, the data are obtained from interviews, and some of the potential

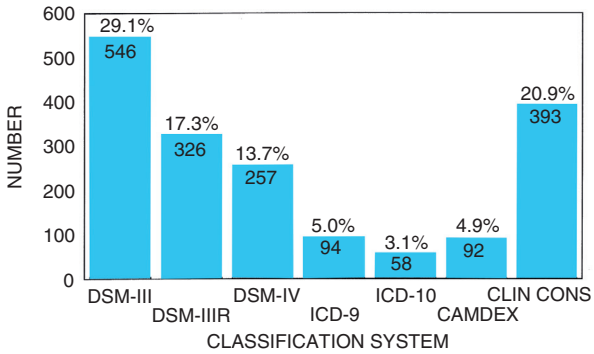

Fig. 3.16 Number of people with and prevalence (%) of dementia in the Canadian Study of Health and Aging cohort (n = 1,879) as diagnosed by different classification systems. The various abbreviations refer to commonly used diagnostic manuals for medical conditions. *CAMDEX,* Cambridge Mental Disorders of the Elderly Examination; *CLIN CONS,* Clinical Consensus; *DSM,* Diagnostic and Statistical Manual of Mental Disorders; *ICD,* International Classification of Diseases. (Data from Erkinjuntti T, Østbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. *N Engl J Med.* 1997;337:1667–1674.)

limitations with interview data are listed in Box 3.2. Ideally, we would have laboratory or other confirmatory evidence to explicitly identify who has the disease. However, often such evidence is not available, and despite these limitations, interview data are extremely valuable in providing information about new cases.

Problems With Denominators

Many factors affect the denominators used. Of these, selective undercounting of certain groups in the population may occur. For example, young men in ethnic minority groups and recent immigrants have been missed in many counts of the population. Frequently, we wish to determine whether a certain group has a higher-than-expected risk of disease so that appropriate preventive measures and financial resources can be directed to that group. We are therefore interested in the rates of disease for different ethnic groups rather than just for the entire population as a whole. There are different ways to classify people by ethnic group, such as by language, country of origin, heritage, or parental ethnicity. When different studies use different definitions, comparison of the results is difficult. What is most important in any study is that the working definition be clearly stated so that the reader can judge whether the results are truly comparable.

In an earlier section, we stated that for a rate to make sense, everyone in the group represented by the denominator must have the potential to enter the group that is represented by the numerator but does not have to actually experience the disease and be in the numerator. Refer to the *at risk* concept earlier in this chapter. The issue is not a simple one. For example, hysterectomy is one of the most commonly performed surgical procedures in the United States. This raises a question

BOX 3.2 Some Possible Sources of Error in Interview Surveys

1. Problems due to difficulties in diagnosis:
   a. The participant may have the disease, but may have no symptoms and may not be aware of the disease.
   b. The participant may have the disease and may have had symptoms, but may not have had medical attention and therefore may not know the name of the disease.
   c. The participant may have the disease and may have had medical attention, but the diagnosis may not have been made or conveyed to the person or the person may have misunderstood.
   d. The participant may not accurately recall an episode of illness or events and exposures related to the illness.
2. Problems associated with the study participant:
   a. The participant may be involved in litigation about the illness and may choose not to respond or may alter his or her response.
   b. The participant may be reluctant to provide accurate information if they have concerns that certain responses may not please the interviewer or may elicit a possible stigma.
   c. The participant is too ill to respond. As a result, either that participant is not included in the study or a surrogate, such as a family member or friend, is interviewed. Surrogates, however, often have incomplete information about the participant's past exposures.
3. Problems associated with the interviewer:
   a. The participant may provide the information, but the interviewer may not record it or may record it incorrectly.
   b. The interviewer may not ask the question they are supposed to ask or may ask it incorrectly.
   c. The interviewer may be biased by knowing the hypothesis being tested and may probe more intensively in one group of participants than in another.

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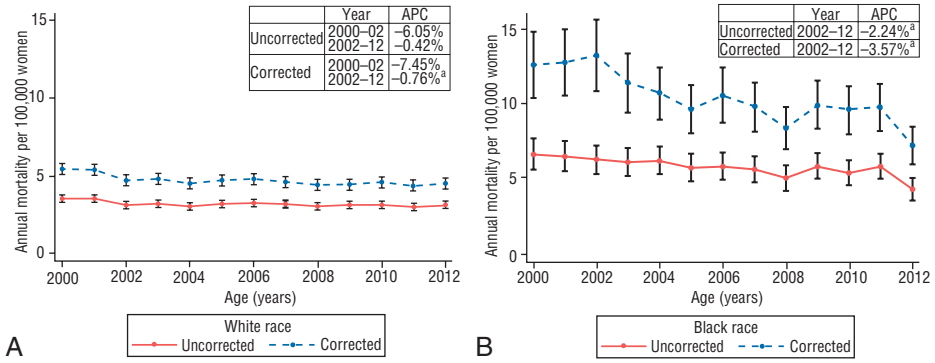

Fig. 3.17 Trends in age-standardized cervical cancer mortality rates, uncorrected and corrected for the prevalence of hysterectomy, from 2000–2012 for (A) White and (B) Black women. [a]The annual percentage change *(APC) P* value was significant at $\alpha < .05$. (From Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. *Cancer*. 2017;123:1044–1050.)

about cervical or endometrial cancer mortality rates. If we include females who have had hysterectomies in the denominator, clearly, they are not at risk for developing cervical or endometrial cancer. Fig. 3.17 shows cervical cancer mortality rates from the United States; both uncorrected rates and rates corrected for hysterectomy are presented. We see that the corrected rates are higher. Why? Because in the corrected rates women who have had hysterectomies are removed from the denominator. Consequently, the denominator gets smaller and the rate increases. However, in this case the trend over time is not significantly changed whether we use corrected or uncorrected rates.

Problems With Hospital Data

Data from hospital records (now often electronic medical records) are one of the most important sources of information for epidemiologic studies in the modern era. However, Box 3.3 lists some of the problems that arise in using hospital data, as one type of *administrative dataset*, for research purposes. First, hospital admissions are selective. They may be selective on the basis of personal characteristics, severity of disease, associated medical conditions, health insurance status of the patient, and admissions policies that vary from hospital to hospital. Second, hospital records are not designed for research but rather for patient care. Records may be incomplete, illegible, or missing. They often include data in narrative format rather than columns and rows that are easily analyzed. The diagnostic quality of the records of hospitals, physicians, and clinical services may differ and may not be consistent over time. Thus, if we want to combine patients from different hospitals, we may have significant problems of comparability. Third, if we wish to calculate rates, we have a problem defining denominators, because most hospitals in the United States do not have defined catchment areas—that is, areas that require that all persons in those areas who are hospitalized be admitted to a particular hospital, and that none from outside the catchment area be admitted to that hospital.

On a lighter note, Box 3.4 lists some notes that were dictated by physicians for inclusion in their patients' medical records.

BOX 3.3 Some Limitations of Hospital Data

1. Hospital admissions are selective in relation to:
   a. Personal characteristics
   b. Severity of disease
   c. Associated conditions
   d. Admission policies
2. Hospital records are not designed for research. They may be:
   a. Incomplete, illegible, or missing
   b. Variable in diagnostic quality
   c. Some data collected in narrative format, not easily exported to columns and rows
3. Population(s) at risk (denominator) is (are) generally not defined

BOX 3.4 Some Notes Dictated by Physicians for Inclusion in Patients' Medical Records

"Patient has two teenage children, but no other abnormalities."
"On the second day the knee was better and on the third day it had completely disappeared."
"Patient was alert and unresponsive."
"When she fainted, her eyes rolled around the room."
"Rectal examination revealed a normal size thyroid."
"By the time he was admitted, his rapid heart had stopped, and he was feeling better."

Relationship Between Incidence and Prevalence

We have said that incidence is a measure of risk and that prevalence is not, because it does not take into account the duration of the disease. However, there is an important relationship between incidence and prevalence: in a steady-state situation, in which the rates are not changing, and in-migration equals out-migration in the populations being examined, and when the prevalence is not too high, the following equation applies:

$$\text{Prevalence} = \text{Incidence} \times \text{Duration of Disease}$$

This is demonstrated in the following hypothetical example. Using chest x-rays, 2,000 persons are screened for TB: 1,000 are upper-income individuals from Hitown and 1,000 are lower-income individuals from Lotown (Table 3.3). X-ray findings are positive in 100 of the Hitown people and in 60 of the Lotown people. Can we therefore conclude that the risk of TB is higher in Hitown people than in Lotown people? Clearly, we cannot, for what we are measuring with a chest x-ray is the point prevalence of disease—we do not know how long any of the people with positive x-rays have had their disease (Table 3.4). We could in fact consider a hypothetical scenario that might explain the higher prevalence in Hitown people that is not related to any higher risk in Hitown people (Table 3.5). We have said that prevalence = incidence × duration. Let us assume that Lotown people have a much higher risk (incidence) of TB than Hitown people—20 cases/year in Lotown people compared with 4 cases/year in Hitown people. But for a variety of reasons, such as poorer access to medical care and poorer nutritional status, Lotown people survive with their disease, on average, for only 3 years, whereas Hitown people survive, on average, for 25 years. In this example, therefore, there is a higher prevalence in Hitown people than in Lotown people, not because the risk of disease is higher in Hitown people, but because affected Hitown people survive longer; the prevalence of disease (incidence × duration) is therefore higher in Hitown people than in Lotown people.

Fig. 3.18 shows the percentage of all births in New Zealand that were extramarital from 1962 to 1979. Much concern was expressed because of the apparent steady rise in extramarital births. However, as seen in Fig. 3.19, there had really been no increase in the rate of extramarital births; there had been a decline in total births that was largely accounted for by a decline in

TABLE 3.3 Hypothetical Example of Chest X-Ray Screening: I. Populations Screened and Numbers With Positive X-Rays

Screened Population	No. With Positive X-Ray
1,000 Hitown	100
1,000 Lotown	60

TABLE 3.4 Hypothetical Example of Chest X-Ray Screening: II. Point Prevalence

Screened Population	No. With Positive X-Ray	Point Prevalence per 1,000 Population
1,000 Hitown	100	100
1,000 Lotown	60	60

TABLE 3.5 Hypothetical Example of Chest X-Ray Screening: III. Prevalence, Incidence, and Duration

Screened Population	Point Prevalence per 1,000	Incidence (Occurrences/Year)	Duration (Years)
Hitown	100	4	25
Lotown	60	20	3

Prevalence = Incidence × Duration

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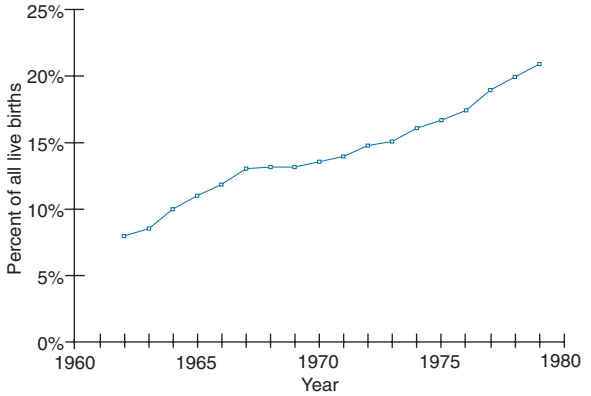

Fig. 3.18 Percentage of births that were extramarital in New Zealand, 1962–79, based on data from the Department of Statistics. (Modified from Benfield J, Kjellstrom T. New Zealand ex-nuptial births and domestic purposes benefits in a different perspective. *N Z Nurs J.* 1981;74:28–31.)

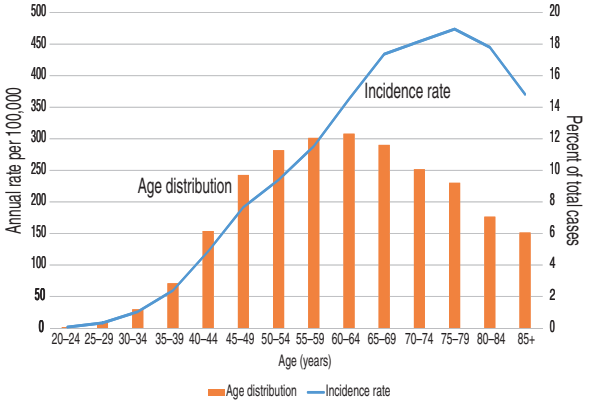

Fig. 3.20 Breast cancer incidence rates in White women and distribution of cases by age, 2000–13. (Data from Surveillance, Epidemiology, and End Results [SEER] Program [www.seer.cancer.gov] SEER*Stat Database: Incidence—SEER 18 Regs Research. Courtesy Dr. Louise Brinton and Mr. Jake Thistle.)

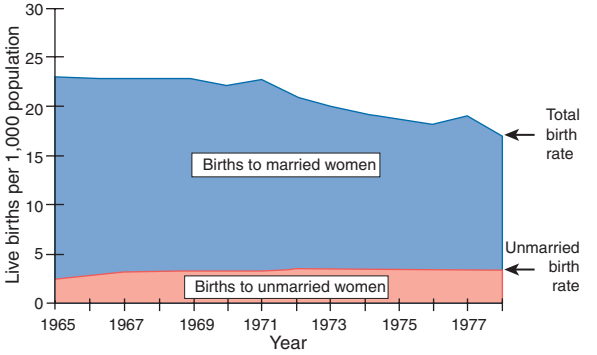

Fig. 3.19 Births to married and unmarried women in New Zealand, 1965–78, based on data from the Department of Statistics. (Modified from Benfield J, Kjellstrom T. New Zealand ex-nuptial births and domestic purposes benefits in a different perspective. *N Z Nurs J.* 1981;74:28–31.)

births to married women. The extramarital births, as a result, accounted for a greater percentage of all births, even though the rate of extramarital births had not increased over the 17-year period.

This example makes two points: First, a proportion is *not* a rate, and we shall return to this point in our discussion of mortality. Second, birth can be viewed as an *event*, just as the development of disease is an event, and appropriate rates can be computed. In discussing babies born with malformations, some people prefer to speak of the prevalence of malformations at birth rather than the incidence of malformations at birth, because the malformation was clearly present (but often unrecognized), even before birth. Furthermore, because some proportion of cases with malformations abort before birth, any estimate of the frequency of malformations at birth is probably a significant underestimate of the true incidence. Hence, the term "prevalence at birth" is often used.

Fig. 3.20 shows breast cancer incidence rates in women by age and the distribution of breast cancer in women by age. Ignore the bar graph for the moment and consider the line curve. The pattern is one of continually increasing incidence with age, with a change in the slope of the curve between ages 45 and 50 years. This change is observed in many countries. It has been suggested that something happens near the time of menopause, and that premenopausal and postmenopausal breast cancer may be different diseases. Note that, even in old age, the incidence or risk of breast cancer continues to rise.

Now let us look at the bar chart—the distribution of breast cancer cases by age. If the incidence is increasing so dramatically with age, why are only fewer than 5% of the cases occurring in the oldest age group of women? The answer is that there are very few women alive in that age group, so that even though they have a very high risk of breast cancer, the group is so small that they contribute only a small proportion of the total number of breast cancer cases seen at all ages. The fact that so

few cases of breast cancer are seen in the older age groups has contributed to a false public impression that the risk of breast cancer is low in these groups and that mammography is therefore not important in older women. This is a serious misperception. The need to change public thinking on this issue is a major public health challenge. We therefore see the importance of recognizing the distinction between the distribution of disease or the proportion of cases, and the incidence rate or risk of the disease.

Geographic Information System

One approach to examining geographic or spatial differences in the distribution of cases, whether incidence or prevalence, is to plot the cases on a map. Mapping the geographic distribution of the cases dates back to the work of Dr. John Snow, an English physician, in the midst of the cholera outbreak in Soho district of London, England, in 1854. Fig. 3.21 shows the map on which Snow plotted the cholera-related deaths and the locations of the city's water pumps. Snow used the map to show that the cholera cases were centered on a water pump on Broad Street, which was operated by a company that took water from a sewage-polluted part of the Thames River.

The science of using maps continued to evolve. The Geographic Information System (GIS) uses a variety of information on the geographic distribution of disease and how it is related to the environment that the people live in, and subsequently identifies *clusters* of diseases or events. This aids policy makers in identifying and prioritizing health problems and resource allocation. However, many apparent clusters are due only to chance, and an important epidemiologic challenge is to investigate such groups of cases and rule out an environmental etiology for what appears to be a greater-than-expected proximity of cases of a disease in time and space, and that is where the role of modern spatial epidemiologic and statistical methods come to work.

Fig. 3.22 shows a map of Baltimore city displaying the violent crimes per 100 residents (color gradient)

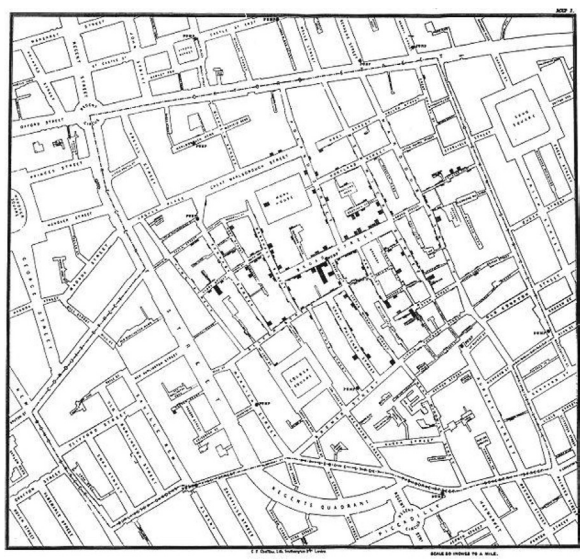

Fig. 3.21 Map of Soho district in London, England, showing clusters of cholera deaths around the Broad Street pump. (Published by C.F. Cheffins, Lith, Southampton Buildings, London, England, 1854 in Snow J. *On the Mode of Communication of Cholera*. 2nd ed. New Burlington Street, London: John Churchill; 1855. https://en.wikipedia.org/wiki/File:Snow-cholera-map-1.jpg.)

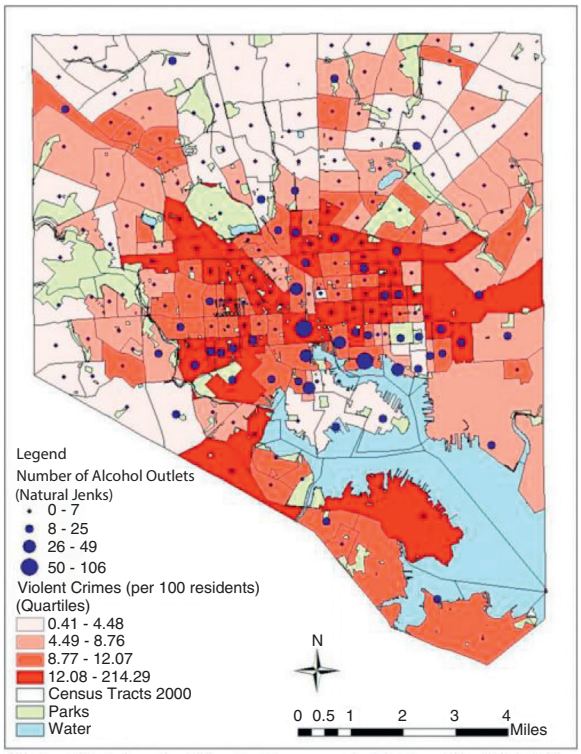

Fig. 3.22 Violent crimes (per 100 residents) per census tract, Baltimore City, 2006–10. (Modified from Jennings JM, Milam AJ, Greiner A, et al. Neighborhood alcohol outlets and the association with violent crime in one mid-Atlantic City: the implications for zoning policy. *J Urban Health*. 2014;91:62–71.)

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per census tract between 2006 and 2010, and the number of alcohol outlets (circles). Using geospatial modeling, the researchers found that the increased numbers of alcohol outlets was associated with increased violent crime in Baltimore. Such findings have very important public health and policy implications. Zoning code policies should take into account how alcohol outlets in residential areas could impact violent crimes. Another example on the utility of spatial epidemiologic tools is presented in Fig.3.23. It shows the Crude COVID-19 incidence in Brazilian municipalities from February 25 to September 26, 2020, which demonstrates the higher the income inequality, the higher the risk of COVID-19 incidence.

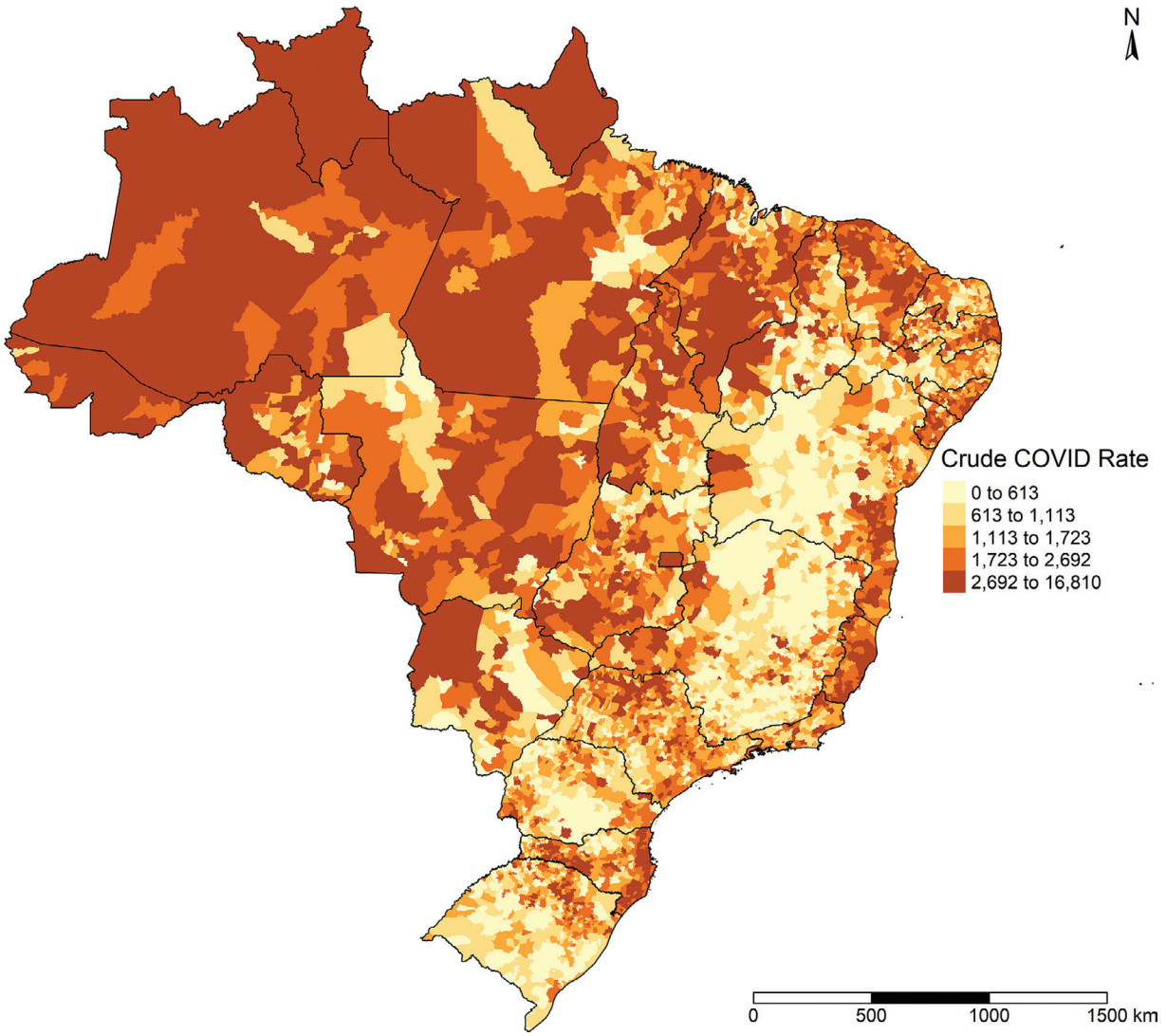

Fig 3.23 Spatial analysis of COVID-19 incidence and the sociodemographic context in Brazil. Crude COVID-19 incidence in Brazilian municipalities, February 25 to September 26, 2020. (From Raymundo CE, Oliveira MC, Eleuterio TA, et al. Spatial analysis of COVID-19 incidence and the sociodemographic context in Brazil. *PLoS One*. 2021;16(3):e0247794).

CONCLUSION

In this chapter, we have emphasized the important role that epidemiology plays in surveillance of diseases in human populations and the importance of surveillance of morbidity for the planning and development of health services. This is especially challenging in developing countries, many of which lack the infrastructure for gathering vital statistics and other routine data on large (representative) populations. We have reviewed different approaches to measuring morbidity, and we have seen that a rate involves specification of a numerator, a denominator of people at risk, and time—either explicitly or implicitly. In the next chapter, we will turn to measuring mortality. In Chapter 5, we will discuss how we use screening and diagnostic tests to identify individuals who are ill (who are included in the numerator) and distinguish them from those in the population who are not ill. In Chapter 18, we will discuss how epidemiology is used for evaluating screening programs.

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REVIEW QUESTIONS FOR CHAPTER 3

1. *At an initial examination in Oxford, Massachusetts, migraine headache was found in 5 of 1,000 men aged 30 to 35 years and in 10 of 1,000 women aged 30 to 35 years. The inference that women have a two times greater risk of developing migraine headache than do men in this age group is:*

- **a.** Correct
- **b.** Incorrect, because a ratio has been used to compare male and female rates
- **c.** Incorrect, because of failure to recognize the effect of age in the two groups
- **d.** Incorrect, because no data for a comparison or control group are given
- **e.** Incorrect, because of failure to distinguish between incidence and prevalence

2. *A prevalence survey conducted from January 1 through December 31, 2012, identified 1,000 cases of schizophrenia in a city of 2 million persons. The incidence rate of schizophrenia in this population is 5/100,000 persons each year. What percentage of the 1,000 cases were newly diagnosed in 2012?* ____

3. *Which of the following is an advantage of active surveillance?*

- **a.** Requires less project staff
- **b.** Is relatively inexpensive to employ
- **c.** More accurate due to reduced reporting burden for health care providers
- **d.** Relies on different disease definitions to account for all cases
- **e.** Reporting systems can be developed quickly

4. *What would be the effect on age-specific incidence rates of uterine cancer if women with hysterectomies were excluded from the denominator of the calculations, assuming that there are some women in each age group who have had hysterectomies?*

- **a.** The rates would remain the same
- **b.** The rates would tend to decrease
- **c.** The rates would tend to increase
- **d.** The rates would increase in older groups and decrease in younger groups
- **e.** It cannot be determined whether the rates would increase or decrease

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5. *A survey was conducted among the nonhospitalized adult population of the United States during 2008 through 2011. The results from this survey are shown below.*

Age Group	Persons With Hypertension (%)
18–29 years	4
30–39 years	10
40–49 years	22
50–59 years	43
60–69 years	54
70 and older	64

The researchers stated that there was an age-related increase in the risk of hypertension in this population. You conclude that the researchers' interpretation:

a. Is correct
b. Is incorrect because it was not based on rates
c. Is incorrect because incidence rates do not describe risk
d. Is incorrect because prevalence is used
e. Is incorrect because the calculations are not age-adjusted

Questions 6 and 7 use the following information:

Population of the city of Atlantis on March 30, 2012 = 183,000
No. of new active cases of TB occurring between January 1 and June 30, 2012 = 26
No. of active TB cases according to the city register on June 30, 2012 = 264

6. *The incidence rate of active cases of TB for the 6-month period was:*
a. 7 per 100,000 population
b. 14 per 100,000 population
c. 26 per 100,000 population
d. 28 per 100,000 population
e. 130 per 100,000 population

7. *The prevalence rate of active TB as of June 30, 2012, was:*
a. 14 per 100,000 population
b. 130 per 100,000 population
c. 144 per 100,000 population
d. 264 per 100,000 population
e. None of the above

8. *Disease X has a duration of 15 years and a low incidence (5 per 100,000 person-years). Disease Y has a duration of 5 years and a low incidence (5 per 100,000 person-years). Comparing Disease X to Y in the same population, we would expect Disease X to have a:*
a. Better cure rate
b. Lower prevalence
c. Higher prevalence
d. Higher incidence
e. Shorter average duration

9. *The following health statistics are available on the Internet for country Z about two disease outcomes. Disease A has an annual incidence of 225 per 100,000 population and an annual mortality rate of 150 per 100,000. Disease B has an annual incidence of 500 per 100,000 population and the same annual mortality rate as disease A. Neither disease A nor B has a cure. What would you conclude regarding the burden of these diseases in country Z?*
a. The proportionate mortality is higher for disease A than disease B
b. The case fatality ratio is higher for disease B than disease A
c. Disease A has a higher prevalence than disease B
d. Disease B has a higher prevalence than disease A
e. Years of potential life lost (YPLL) is greater for disease B than disease A

10. *Chikungunya virus infection was recently introduced into the Dominican Republic. During the first year after introduction, the virus has infected a total of 251,880 people in the Dominican Republic, which has a population size of 10.4 million people. Infection by the chikungunya virus is rarely fatal. Which of the following is correct?*
a. The incidence of chikungunya infection is 251,880 per year
b. The prevalence of chikungunya infections is 251,880
c. The mortality rate of chikungunya is 24.2 per 1,000 persons
d. The 1-year cumulative incidence of chikungunya is 24.2 per 1,000 persons
e. The cumulative survival from chikungunya infections is 24.2 per 1,000 persons

4

The Occurrence of Disease: II. Mortality and Other Measures of Disease Impact

You do not die from being born, nor from having lived, nor from old age. You die from something. ... There is no such thing as a natural death: Nothing that happens to a man is ever natural, since his presence calls the world into question. All men must die: but for every man his death is an accident and, even if he knows it and consents to it, an unjustifiable violation.

***— Simone de Beauvoir, writing of her mother's death, in A Very Easy Death*[1]**

LEARNING OBJECTIVES

- To compare different measures of mortality, including mortality rates, case-fatality, proportionate mortality, and years of potential life lost.
- To show when mortality can approximate the risk of disease.
- To introduce issues that arise in comparing mortality across two or more populations.
- To define, calculate, and interpret direct and indirect age-adjusted mortality rates.
- To introduce other measures of disease impact.

Mortality is of great interest for several reasons. First of all, death is the ultimate experience that every human being is destined to experience. Death is clearly of tremendous importance to each person, including questions of when and how death will occur and whether there is any way to delay it. From the standpoint of studying disease occurrence, expressing mortality in quantitative terms can pinpoint differences in the risk of dying from a disease between people in different geographic areas and subgroups in the population. Mortality rates can serve as measures of disease severity and can help us determine whether the treatments for a disease have become more effective over time. In addition, given the problem that often arises in identifying new cases of a disease, mortality rates may serve as surrogates for incidence rates when the disease being studied is a severe and lethal one (that is, of short duration between detection and death). This chapter will address the quantitative expression of mortality and the uses of such measures in epidemiologic studies.

MEASURES OF MORTALITY

Fig. 4.1 shows the number of cancer deaths from 1999 to 2019 in the United States. Clearly, the absolute *number* of people dying from cancer is seen increasing significantly through the year 2019, but from this graph, we cannot say that the *risk* of dying from cancer is increasing, because the only data that we have in this graph are numbers of deaths (numerators); we do not have denominators (populations at risk). If, for example, the size of the US population is also increasing at the same rate, the risk of dying from cancer does not change.

For this reason, if we wish to address the risk of dying, we must deal with rates. Fig. 4.2 shows mortality rates for several types of cancer in men from 1930 to 2018. Note that the rates are expressed as deaths per 100,000 population. The most dramatic increase is in deaths from lung cancer. This increase is clearly of epidemic proportions and, tragically, lung cancer is a

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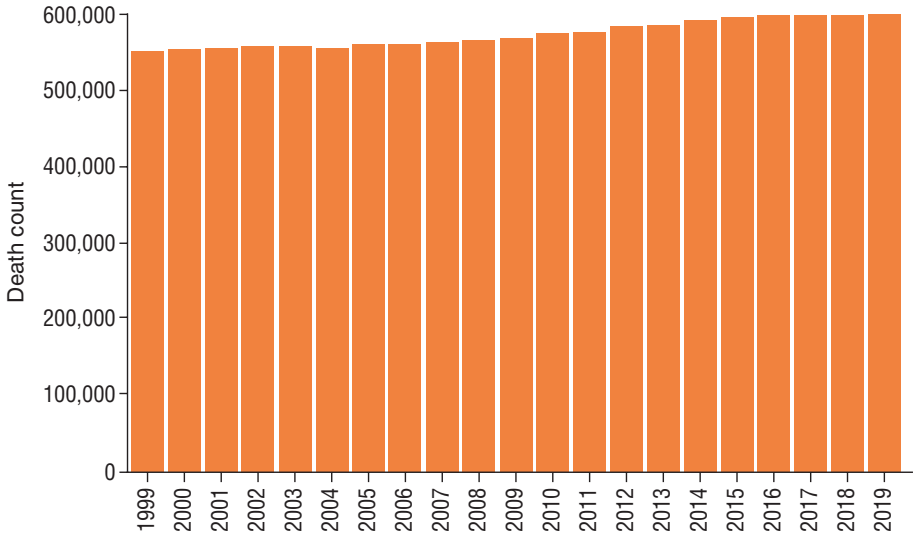
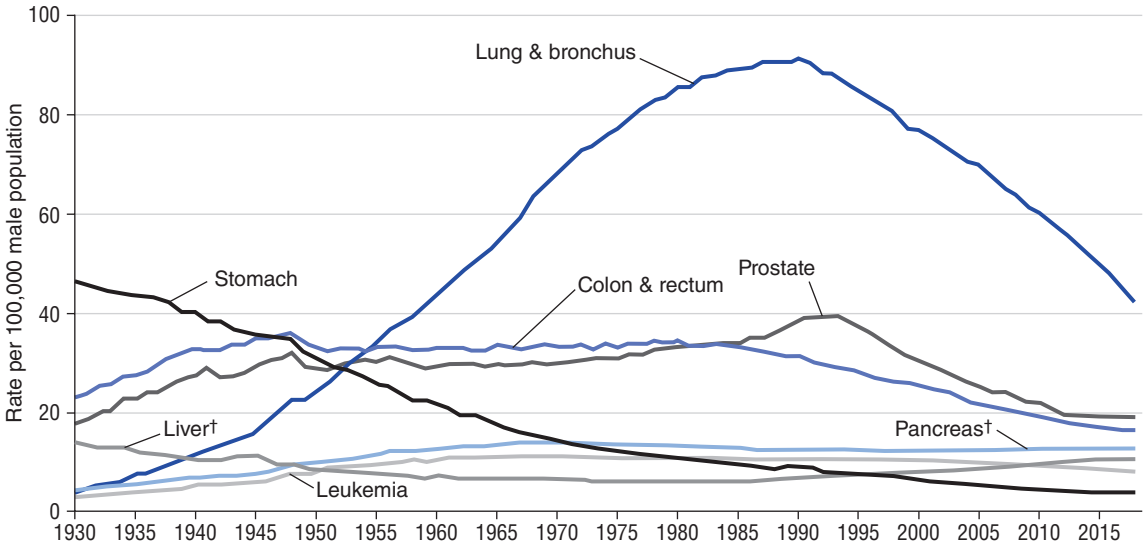


Fig. 4.1 Annual number of cancer deaths, 1999–2019. (From Centers for Disease Control and Prevention. United States Cancer Statistics: Data Visualizations. URL: https://gis.cdc.gov/Cancer/USCS/#/Trends/).



*Per 100,000, age adjusted to the 2000 US standard population.
†Mortality rates for pancreatic and liver cancers are increasing.
Note: Due to changes in ICD coding, numerator information has changed over time for cancers of the liver, lung and bronchus, and colon and rectum.

Fig. 4.2 Trends in age-adjusted cancer death rates* by site, males, US, 1930–2018. *ICD,* International Classification of Diseases. (From US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2018, National Center for Health Statistics, Centers for Disease Control and Prevention. © 2021, American Cancer Society, Inc., Surveillance Research.)

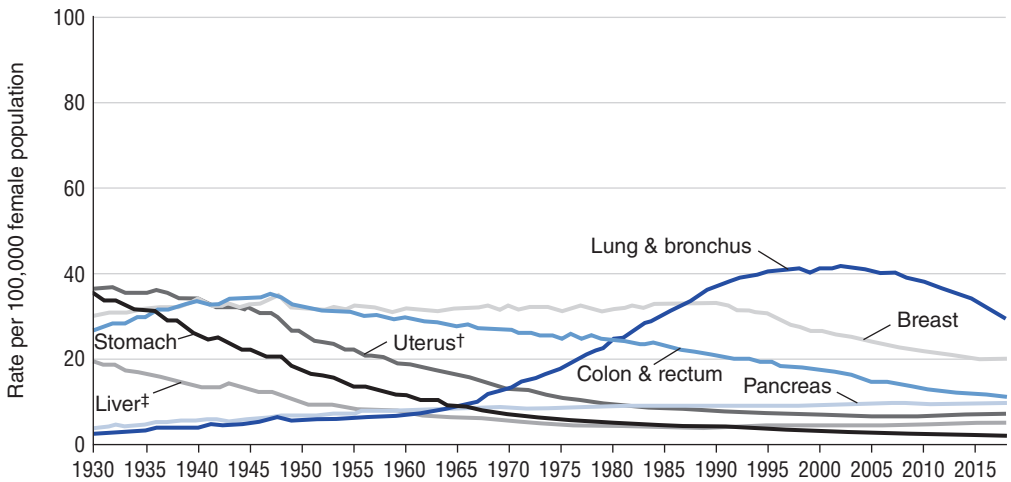
preventable cause of death. Fortunately, since the mid-1990s, lung cancer mortality has declined, paralleling earlier decreases in rates of smoking among men. Other cancers are also of interest. Age-adjusted mortality from prostate cancer also peaked in the mid-1990s and has declined since. Cancers of the colon and rectum have declined over many years (no doubt attributable to the expansion of screening to detect these cancers at an earlier stage). The rate of death from stomach cancer has declined dramatically since 1930, although the precise explanation is not known. It has been suggested that the decline may be the result of the increased availability of refrigeration, which decreased the need to smoke foods and thereby decreased human exposure to carcinogens produced in the smoking process. Another possible cause is improved hygiene, which may have reduced the incidence of *Helicobacter pylori* infections that have been implicated in the etiology (or cause) of stomach cancer.

Fig. 4.3 shows a similar presentation for cancer mortality in women for the period 1930 to 2018. Breast cancer mortality remained at essentially the same level for many years but has declined since the early 1990s until 2018. It would be desirable to study changes in the incidence of breast cancer. Such a study is difficult, however, because with aggressive public education campaigns encouraging women to have mammograms and perform breast self-examination, many breast cancers may be detected today at much earlier stages that might have gone undetected years ago. Nevertheless, available evidence suggests that the true incidence of breast cancer in women may have increased for many years but then decreased from 2001 to 2018.

Uterine cancer mortality has declined, perhaps because of earlier detection and diagnosis. Lung cancer mortality in women has increased, and lung cancer has exceeded breast cancer as a cause of death in women. Lung cancer is almost completely preventable, being mostly due to a lifestyle habit, cigarette smoking, which has been voluntarily adopted by many women; today it is the leading cause of cancer death in women in the United States.

We may be particularly interested in mortality relating to age. Fig. 4.4 shows death rates from cancer and from heart disease for people younger than 65 and for those 65 or older. Cancer is the leading cause of death in men and women younger than 65 years, but above age 65, heart disease clearly exceeds cancer as a cause of death.

Fig. 4.5 shows the causes of death worldwide for children younger than 5 years in 2019. The leading



*Per 100,000, age adjusted to the 2000 US standard population. Rate exclude deaths in Puerto Rico and other US territories.
†Uterus refers to uterine cervix and uterine corpus combined.
‡The mortality rates for liver cancer is increasing.
Note: Due to changes in ICD coding, numerator information has changed for cancers of the liver, lung and bronchus, colon and rectum, and uterus

Fig. 4.3 Trends in age-adjusted cancer death rates* by site, females, US, 1930–2018. *ICD,* International Classification of Diseases. (From US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2018, National Center for Health Statistics, Centers for Disease Control and Prevention. © 2021 American Cancer Society, Inc., Surveillance Research.)

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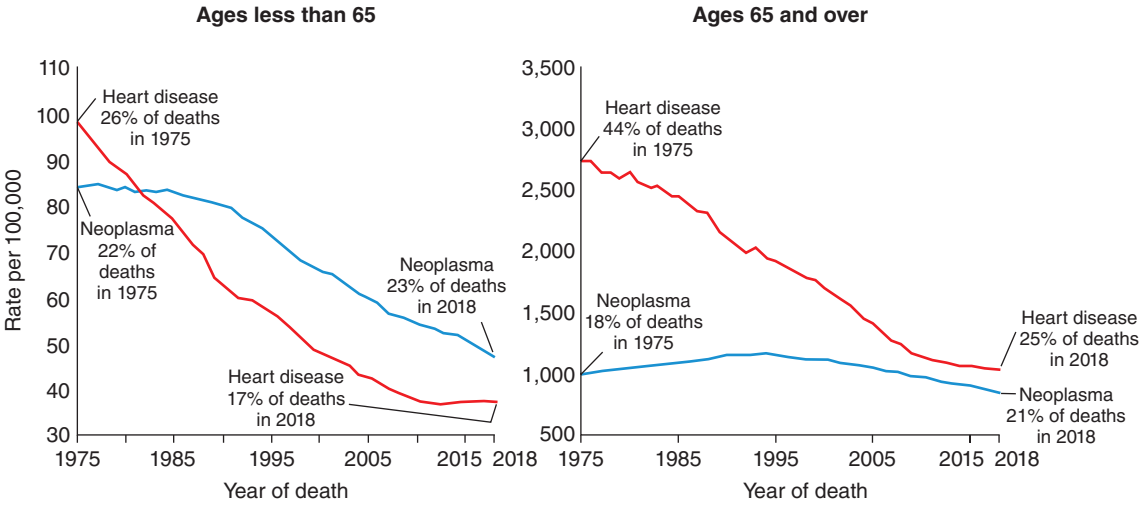

Rates are per 100,000 and age-adjusted to the 2000 US Std population (19 age groups - Census P25-1103).

Fig. 4.4 US death rates, 1975–2018 heart disease compared to neoplasms, by age at death. (From US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention.)

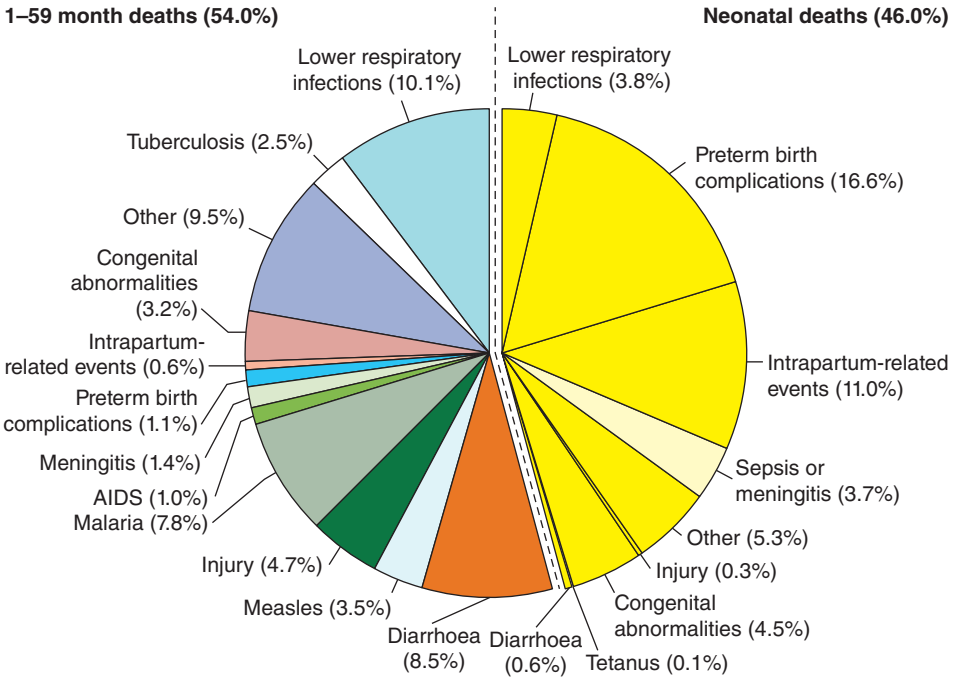

Fig. 4.5 Global causes of under-5 deaths in 2019. Deaths of neonates (aged 0–27 days) are on the right-hand side and deaths of children aged 1–59 months are on the left-hand side. (From Perin J, Mulick A, Yeung D, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet Child Adolesc Health.* 2022;6(2):106–115.)

causes of death among children under 5 years of age in 2019 were preterm birth complications, lower respiratory infections, intrapartum-related complications, diarrhea, and congenital abnormalities. Neonatal deaths accounted for 46% of under-5 deaths in 2019. Infectious diseases accounted for over half of the 5.9 million deaths of children under age 5, with the largest percentages due to lower respiratory infections, diarrhea, and malaria.

Mortality Rates

How is mortality expressed in quantitative terms? Let us examine some types of mortality rates. The first is the annual death rate, or mortality rate, from all causes combined:

$$\text{Annual mortality rate for all causes (per 100,000 population)} = \frac{\text{Total no. of deaths from all causes in 1 year}}{\text{No. of persons in the population at midyear}} \times 100{,}000$$

Note that because the population changes over time, the number of persons in the population at midyear is generally used as an approximation of average population in that year.

The same principles mentioned in the discussion of morbidity apply to mortality; for a mortality rate to make sense, anyone in the group represented by the denominator must have the potential to enter the group represented by the numerator.

We may not always be interested in a rate for the entire population; perhaps we are interested only in a certain age group, in men or in women, or in one ethnic group. Thus, if we are interested in mortality in children younger than 10 years, we can calculate a rate specifically for that group:

$$\text{Annual mortality rate from all causes for children younger than 10 years of age (per 1,000 population)} = \frac{\text{No. of deaths from all causes in 1 year in children younger than 10 years of age}}{\text{No of children in the population younger than 10 years of age at midyear}} \times 1{,}000$$

In putting a restriction on age, for example, the same restriction must apply to *both* the numerator and the denominator, so that every person in the denominator group will be at risk for entering the numerator group. When such a restriction is placed on a rate, it is called a *specific rate*. The above rate, then, is an *age-specific mortality rate*.

We could also place a restriction on a rate by specifying a diagnosis, and thus limit the rate to deaths from a certain disease, that is, a *disease-specific* or a *cause-specific rate*. For example, if we are interested in mortality from lung cancer, we would calculate it in the following manner:

$$\text{Annual mortality rate from lung cancer (per 1,000 population)} = \frac{\text{No. of deaths from lung cancer in 1 year}}{\text{No. of persons in the population at midyear}} \times 1{,}000$$

We can also place restrictions on more than one characteristic simultaneously, for example, age and cause of death, as follows:

$$\text{Annual mortality rate from leukemia in children} < 10 \text{ years of age (per 1,000 population)} = \frac{\text{No. of deaths from leukemia in 1 year in children} < 10 \text{ years of age}}{\text{No. of children in the population} < 10 \text{ years of age at midyear}} \times 1{,}000$$

Time must also be specified in any mortality rate, in the case above, in one year (which is usually included in the title, e.g., 2022). Mortality can be calculated over 1 year, 5 years, or longer. The period selected is arbitrary, but it must be specified precisely.

Case-Fatality

We must distinguish between a *mortality rate* and *case-fatality*. Case-fatality is calculated as follows:

$$\text{Case-fatality (\%)} = \frac{\text{No. of individuals dying during a specified period of time after disease onset or diagnosis}}{\text{No. of individuals with the specified disease}} \times 100$$

In other words, what percentage of people *who have a certain disease* die within a certain time after their disease was diagnosed? Ideally, we would like to use the date of disease onset as the beginning of the time period specified in the numerator. However, date of disease

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onset is often hard to standardize since many diseases develop insidiously (without symptoms) over a long period of time. As a result, in many chronic diseases, it may be difficult to determine precisely when the disease process began. For example, many patients with arthritis cannot recall when their joint pain first began. In practice therefore we often use date of diagnosis as a surrogate measure for date of disease onset because the exact date of diagnosis can generally be documented from available medical records (note, however, that the medical record is only as reliable as the person entering the data). If the information is to be obtained from respondents, it is worth noting that if the disease in question is a serious one, the date on which the diagnosis was given may well have been a life-changing date for the patient and not easily forgotten.

What is the difference between case-fatality and a mortality rate? In a mortality rate, the denominator represents the entire population at risk of dying from the disease, including both those who have the disease and those who do not have the disease (but who are *at risk* of developing the disease). In case-fatality, however, the denominator is limited to those who *already have the disease*. Thus, case-fatality is a measure of the *severity* or *fatality* of the disease. It can also be used to measure any benefits of a new therapy; as therapy improves, case-fatality would be expected to decline.

The numerator of case-fatality should ideally be restricted to deaths *from that disease*. However, it is not always easy to distinguish between deaths from that disease and deaths from other causes. For example, a person with alcohol-use disorder may die in a car accident; however, the death may or may not be related to alcohol intake.

Let us look at a hypothetical example to clarify the difference between mortality and case-fatality (Box 4.1).

BOX 4.1 Comparison of Mortality Rate With Case-Fatality in the Same Year

Assume a population of 100,000 people of whom 20 are sick with disease X, and in 1 year, 18 of the 20 die from disease X

$$\text{Mortality rate from disease } X = \frac{18}{100{,}000} = 0.00018, \text{ or } 0.18\%$$

$$\text{Case-fatality from disease } X = \frac{18}{20} = 0.9, \text{ or } 90\%$$

Assume that in a population of 100,000 persons, 20 have disease X. In 1 year, 18 people die from that disease. The mortality is very low (0.018%) because the disease is rare; however, once a person has the disease, their chances of dying are great (90%).

Since case-fatality traditionally does not include a time unit, it is considered a proportion, but commonly *mistakenly* reported as *rate*.

Proportionate Mortality

Another commonly used measure of mortality is proportionate mortality, which is not a rate. The proportionate mortality from cardiovascular disease in the United States in 2014 is defined as follows:

$$\text{Proportionate mortality from cardiovascular diseases in the US in 2014 (\%)} = \frac{\text{No. of deaths from cardiovascular diseases in the US in 2014}}{\text{Total deaths in the US in 2014}} \times 100$$

In other words, of all deaths in the United States, what *proportion* was caused by cardiovascular disease? Fig. 4.6 shows proportionate mortality from heart disease in the total population and by race. In each age group, the full bar represents all deaths (100%), and deaths from heart disease are indicated by the dark blue portion. We see that the *proportion* of deaths from heart disease increases with age. However, this does not tell us that the *risk* of death from heart disease is also increasing. This is demonstrated in the following examples.

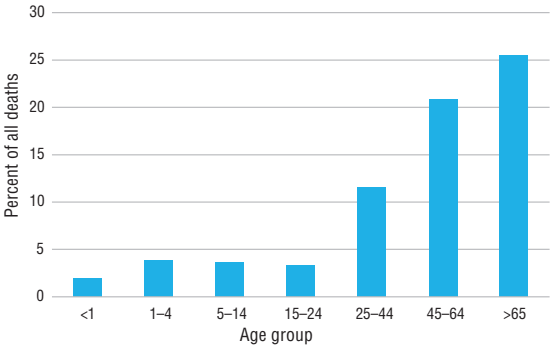

Fig. 4.6 Deaths from heart disease as a percentage of deaths from all causes, by age group, United States, 2014. (From National Center for Health Statistics [NCHS]. *Data from Health, United States, 2015, With Special Feature on Racial and Ethnic Health Disparities*. Hyattsville, MD: NCHS; 2016.)

Table 4.1 shows all deaths and deaths from heart disease in two communities, A and B. All-cause mortality in community A is twice that in community B. When we look at proportionate mortality, we find that 10% of the deaths in community A and 20% of the deaths in community B are due to heart disease. Does this tell us that the risk of dying from heart disease is twice as high in community B as it is in A? The answer is no. When the mortality rates from heart disease are calculated for the two communities (10% of 30/1,000 and 20% of 15/1,000), we find that the mortality rates are identical.

If we observe a change in proportionate mortality from a certain disease over time, the change may be due not to changes in mortality from that disease, but to changes in the mortality of some other disease. Let us consider a hypothetical example: in Table 4.2, we see mortality rates from heart disease, cancer, and other causes in a population in an early period and a later period. First, compare the mortality rates in the two time periods: mortality from heart disease doubled over time (from 40/1,000 to 80/1,000), but mortality rates from cancer and from all other causes (20/1,000) did not change. However, if we now examine the proportionate mortality from each cause, we see that the proportionate mortality from cancer and from other causes has decreased in the population, but only because the proportionate mortality from heart disease has increased. Thus, if the proportion of one segment of the mortality "pie" increases, there will necessarily be a decrease in the proportion of some other segment (Fig. 4.7). Another view of this is seen in Fig. 4.8.

TABLE 4.1 Comparison of Mortality Rate and Proportionate Mortality: I. Deaths From Heart Disease in Two Communities

	Community A	Community B
Mortality rate from all causes	30/1,000	15/1,000
Proportionate mortality from heart disease	10%	20%
Mortality rate from heart disease	3/1,000	3/1,000

TABLE 4.2 Hypothetical Example of Mortality Rates and Proportionate Mortality in Two Periods

	EARLY PERIOD		LATER PERIOD	
Cause of Death	Mortality Rate	Proportionate Mortality	Mortality Rate	Proportionate Mortality
Heart disease	40/1,000	50%	80/1,000	66.7%
Cancer	20/1,000	25%	20/1,000	16.7%
All other causes	20/1,000	25%	20/1,000	16.7%
All deaths	80/1,000	100%	120/1,000	100.0%

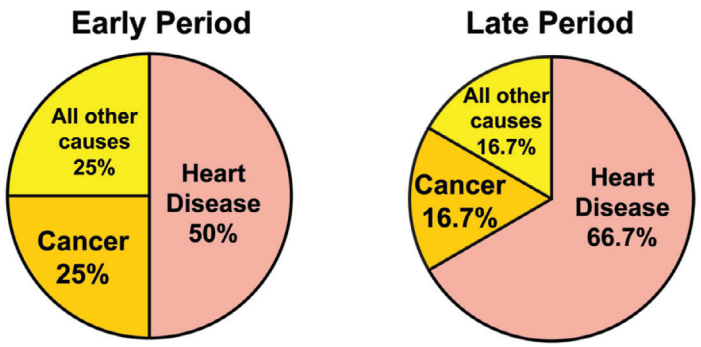

Fig. 4.7 Hypothetical example of proportionate mortality: changes in proportionate mortality from heart disease, cancer, and other causes from the early period to the late period.

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Fig. 4.8 Understanding proportionate mortality. (Family Circus © 2002 Bill Keane, Inc. Distributed by King Features Syndicate, Inc.)

TABLE 4.3 Comparison of Mortality Rate and Proportionate Mortality: II. Deaths From Heart Disease in Two Communities

	Community A	Community B
Mortality rate from all causes	20/1,000	10/1,000
Proportionate mortality from heart disease	30%	30%
Mortality rate from heart disease	6/1,000	3/1,000

As seen in the example in Table 4.3, if all-cause mortality rates differ, cause-specific mortality rates can differ significantly, even when the proportionate mortality is the same. Thus, these examples show that, although proportionate mortality can give us a quick look at the major causes of death, it cannot tell us the risk of dying from a disease. For that, we need a mortality rate.

Years of Potential Life Lost

Another mortality index, years of potential life lost (YPLL), has been increasingly used for setting health priorities. YPLL is a measure of premature mortality, or early death. YPLL recognizes that death occurring in a person at a younger age clearly involves a greater loss of future productive years than death occurring at an older age. Two steps are involved in this calculation: in the first step, for each cause, each deceased person's age at death is subtracted from a predetermined (or "average") age at death. In the United States, this predetermined "standard" age is usually 75 years. Thus, an infant dying at 1 year of age has lost 74 years of life (75 to 1), but a person dying at 50 years of age has lost 25 years of life (75 to 50). Thus, the younger the age at which death occurs, the more years of potential life are lost. In the second step, the "*years of potential life lost*" for each individual are then added together to yield the total YPLL for the specific cause of death. When looking at reports that use YPLL, it is important to note what assumptions the author has made, including what predetermined standard age has been selected.

Fig. 4.9 shows the YPLL in the United States before age 75 years in 2020. The top bar shows the total YPLL from all causes (100%), and the bars below show the individual YPLL from each leading cause of death, with the percentage of YPLL from all causes for which it accounts. We see that the greatest single source of YPLL was unintentional injuries, which, in the same year, was the fourth leading cause of death by its mortality rate (see Fig. 1.2 and Table 1.1). In 2020, the ranking of malignant neoplasms by its mortality rate was second, while its ranking by YPLL was second. This discrepancy results from the fact that injury is the leading cause of death up to age 34 years, and therefore it accounts for a large proportion of YPLL.

Fig. 4.10 shows YPLL from unintentional injuries before age 75 years. We see that the YPLL from motor vehicle traffic accidents accounts for over one fourth of the YPLL. Thus, if we want to have an impact on YPLL, we should address this specific cause of injury related to motor vehicles.

Table 4.4 shows a ranking of causes of death in the United States for 2020 by YPLL, together with crude number of deaths for each cause. By cause-specific number of deaths, suicide is ranked seventh, but by YPLL, it ranked fourth. This reflects the fact that a large proportion of suicide-related deaths occur in young persons.

YPLL can assist in three important public health functions: establishing research and resource priorities,

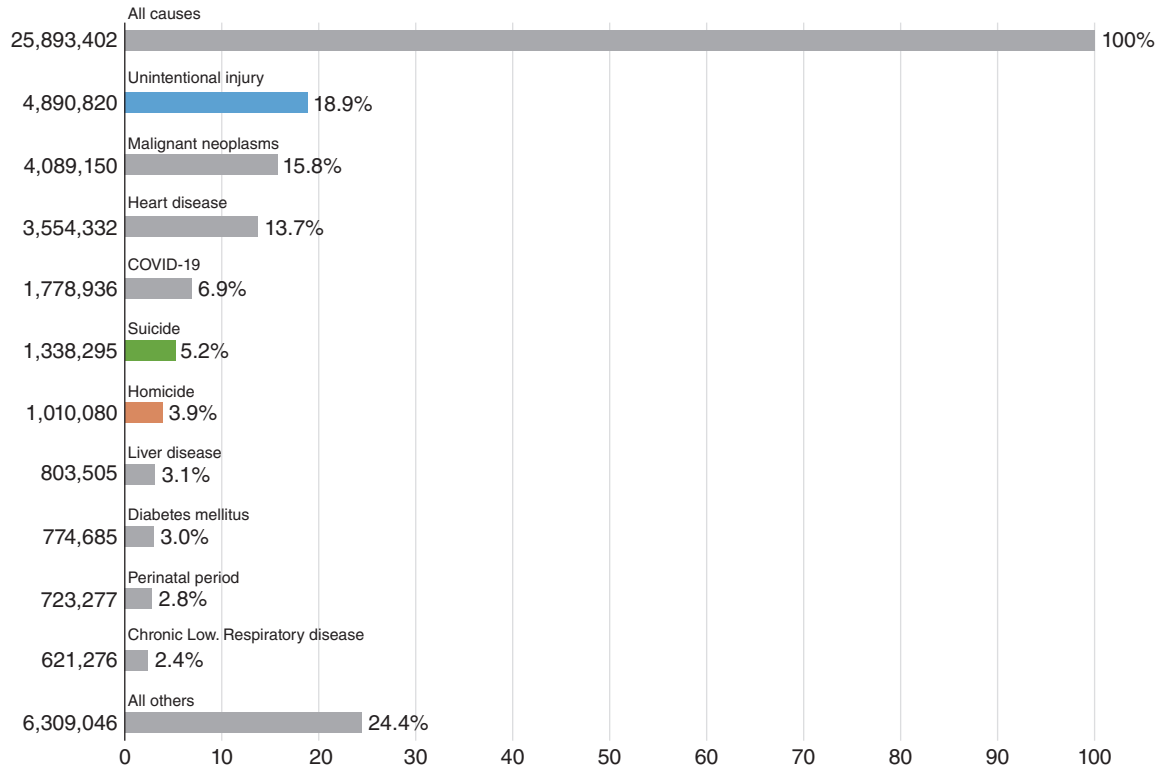

Fig. 4.9 Years of potential life lost (YPLL) before age 75 for 10 leading causes of death 2020, United States, both sexes, all races. (From Centers for Disease Control and Prevention. WISQARS Leading Causes of Death Visualization Tool. URL: https://wisqars.cdc.gov/data/lcd/home)

surveillance of temporal trends in premature mortality, and evaluating the effectiveness of program interventions.[2]

Why Look at Mortality?

Mortality is clearly an index of the severity of a disease from both clinical and public health standpoints, but mortality can also be used as an index of the risk of disease, as shown in Figs. 4.2 and 4.3. In general, mortality data are easier to obtain than incidence data for a given disease, and it therefore may be more feasible to use mortality data as a proxy indicator for incidence. In addition, and unless you are interested in cause-specific mortality, mortality data does not need adjudication or standardization, since all individuals being studied can either be classified as alive or dead. However, when a disease is mild and not fatal, mortality may not be a good index of incidence. A mortality rate is a good reflection of the incidence rate under two conditions: first, when the case-fatality is high (as in untreated rabies), and second, when the duration of disease (survival) is short (as in COVID-19). Under these conditions, mortality is a good measure of incidence, and thus a measure of the risk of disease. For example, cancer of the pancreas is a highly lethal disease: death generally occurs within a few months of diagnosis, and long-term survival is rare. Thus, unfortunately, mortality from pancreatic cancer is a good surrogate for incidence of the disease.

Fig. 4.11 shows mortality trends in the United States from 2000 to 2017 by race. It is evident that the mortality rates for Black and White individuals have gone down, but yet there is a clear disparity between the two races, as shown by the consistent gap between the two curves. Fig. 4.12 shows mortality trends in the United States from 1955 to 2019 by gender and age group. In both panels for males and females, we can see that there

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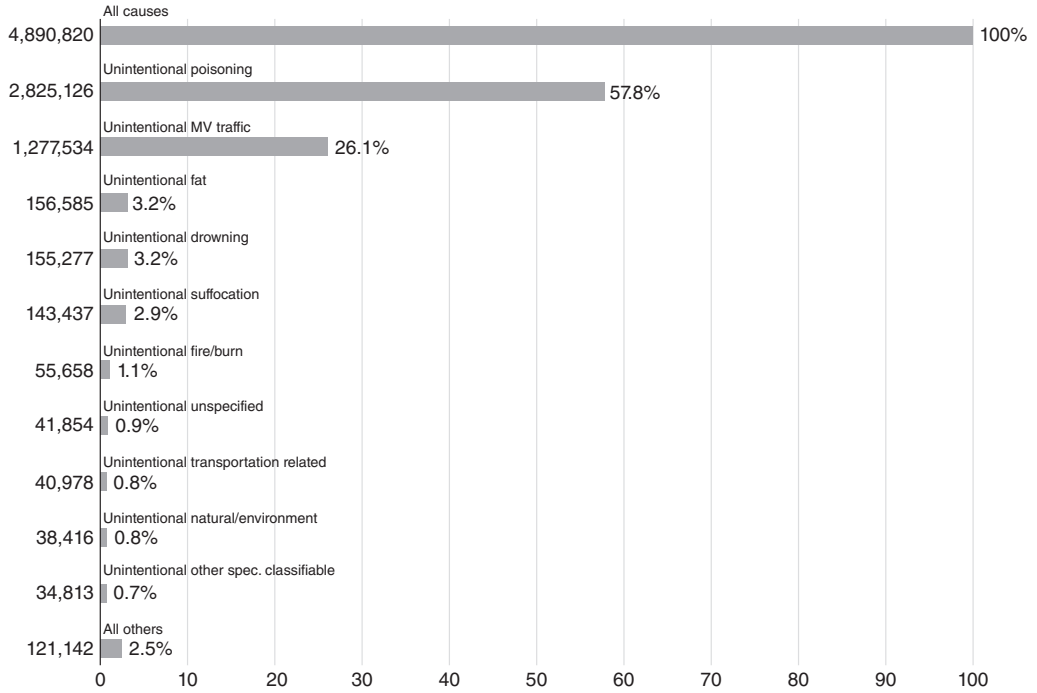


Fig. 4.10 Years of potential life lost (YPLL) before age 75 for 10 leading causes of unintentional injury death 2020, United States, both sexes, all races. (From Centers for Disease Control and Prevention. WISQARS Leading Causes of Death Visualization Tool. URL: https://wisqars.cdc.gov/data/lcd/home)

TABLE 4.4 Estimated YPLL Before Age 75 Years and Age-Adjusted Mortality Rates per 100,000 Persons, by Cause of Death, United States, 2020

Cause Category	Number of Deaths in 2020	YPLL
Heart Disease	696,962	1,443,729
Malignant Neoplasms	602,350	1,542,327
Covid-19	350,831	708,789
Unintentional Injury	200,955	3,403,047
Cerebrovascular	160,264	244,796
Chronic Low. Respiratory Disease	152,657	188,007
Diabetes Mellitus	102,188	330,236
Influenza & Pneumonia	53,544	143,931
Nephritis	52,547	103,656
Liver Disease	51,642	409,897
Suicide	45,979	942,431
Hypertension	41,907	71,390
Homicide	24,576	771,608
Benign Neoplasms	16,229	36,157

YPLL, Years of potential life lost.
Data from Centers for Disease Control and Prevention. WISQARS™ Web-based Injury Statistics Query and Reporting System. www.cdc.gov/injury/wisqars/

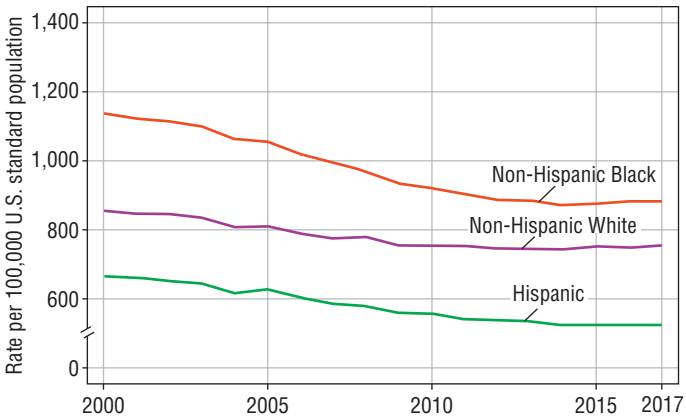
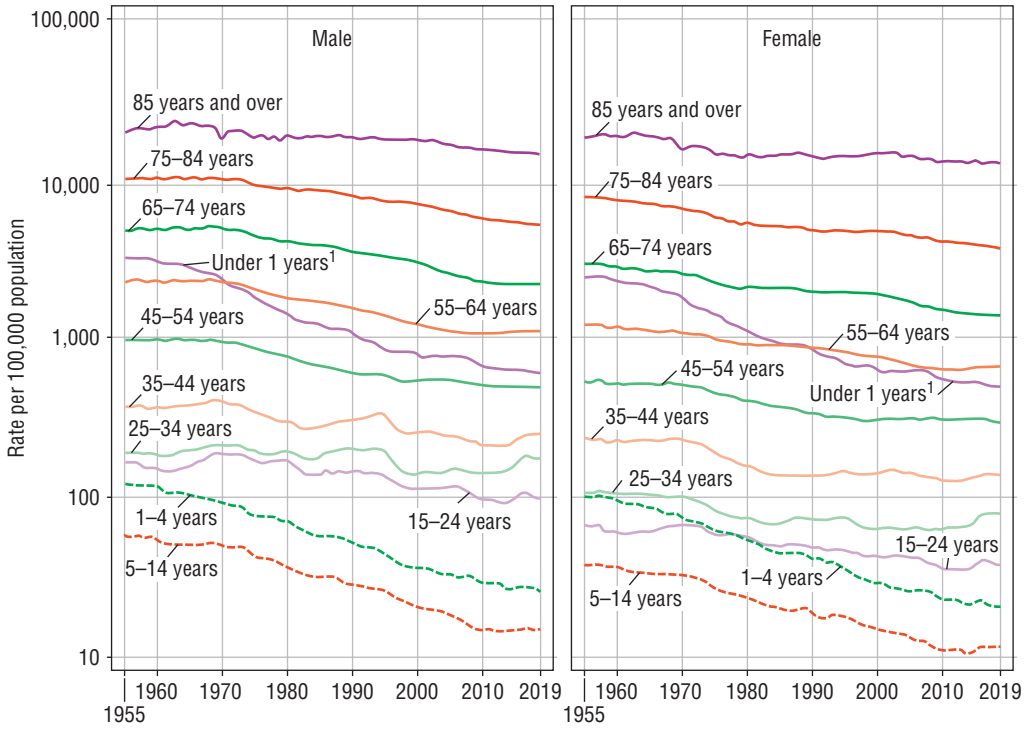


Fig. 4.11 Age-adjusted death rates, by race and Hispanic origin: United States, 2000–2017. (From Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: Final data for 2017. National Vital Statistics Reports 68 (9). US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. National Vital Statistics Systems; June 24, 2019.)



[1]Rates are based on population estimates which differ from infant mortality rates (based on live births), see Figure 5 in this report for infant mortality rates and Technical Notes in this report for more discussion of the difference.

Fig. 4.12 Death rates, by age and sex: United States, 1955–2019. (From Xu J, Murphy SL, Kochanek, KD, Arias E. Deaths: Final data for 2019. National Vital Statistics Reports 70 (8). US Department of Health and Human Services. Center for Disease Control and Prevention. National Center for Health Statistics. National Vital Statistics Systems. July 26, 2021.)

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is a steady decline in the death rate throughout the years, particularly in the age groups less than 14 years. This could be potentially attributed to the widespread coverage of childhood vaccinations. On the other hand, the decline was more modest in the age groups 45 to 64 years due to improvements in the early detection of cardiovascular diseases and cancer, and the evolving new effective treatments. If we look at the left panel for males, we see an increase in the mortality rate for age groups 25 to 44 years in the 1980s, followed by a sharp decline in the early 1990s. This can be explained by the then-emerging human immunodeficiency virus (HIV) disease, and followed by the newly introduced, highly active antiretroviral therapy in the mid-1990s, as well as lifestyle changes resulting from public health education.

A comparison of mortality and incidence is seen in Figs. 4.13 and 4.14. Fig. 4.13 shows breast cancer rates by year in selected European countries from 1975 to 2020. During this period, the age-standardized rates per 100,000 increased in all countries shown in the figure. This increase has been attributed to early detection and improved diagnostic modalities. As seen in Fig. 4.14, however, death rates from breast cancer in selected countries decreased markedly during the 1990s onward, perhaps as a result of earlier detection and increasingly prompt medical and surgical intervention.

Fig. 4.15 presents recent data on time trends in incidence and mortality from breast cancer in Black women and White women in the United States. Compare the time trends in incidence and mortality. What do these curves tell us about new cases of breast cancer over time and survival from breast cancer? Compare the experiences of Black women and White women with regard to both incidence and mortality. How can we describe the differences, and what could be some of the possible explanations?

A final example relates to reports in recent years that the incidence of thyroid cancer in the United States has been increasing. One of two possible explanations is likely. The first explanation is that these reports reflect a

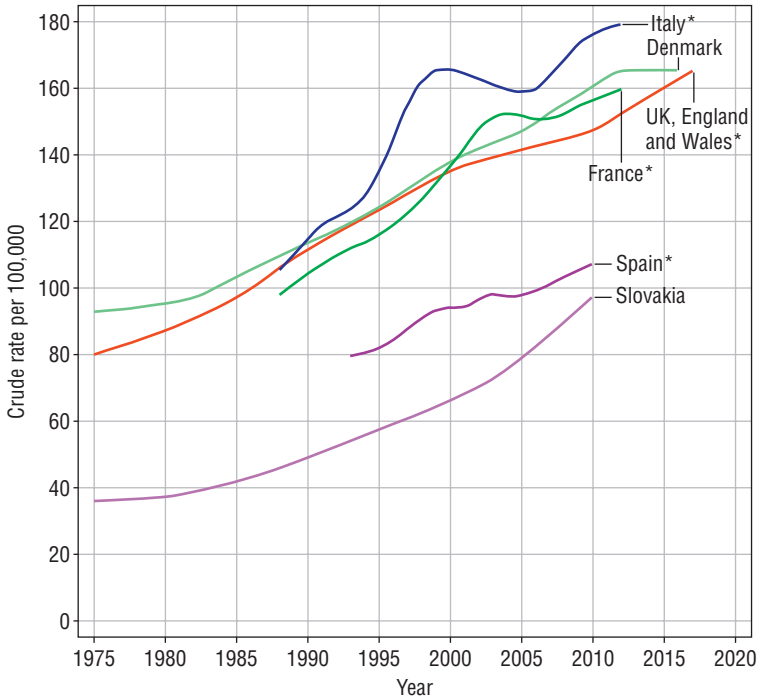
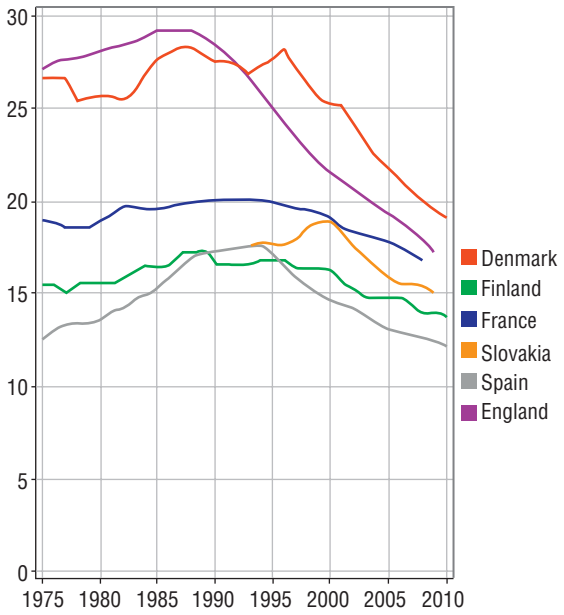


Fig. 4.13 Breast Cancer rate per 100,000, incidence. (From Cancer Over Time. International Agency for Research on Cancer. World Health Organization https://gco.iarc.fr/overtime/en/dataviz © 2022.)



WHO (www.who.int/healthinfo/en/)

Fig. 4.14 Breast Cancer per 10,000, mortality. (From Cancer Over Time. International Agency for Research on Cancer. World Health Organization https://gco.iarc.fr/overtime/en/dataviz © 2022.)

true increase in incidence that has resulted from increases in prevalence of risk factors for the disease. The second explanation is that the reported increased incidence is only an increase in *apparent* incidence. It does not reflect any true increase in new cases but rather an increase in the early detection and diagnosis of subclinical cases, because new diagnostic methods permit us to identify small and asymptomatic thyroid cancers that could not be detected previously.

In order to distinguish between these two possible explanations, Lim et al.[3] studied changes in incidence and mortality from thyroid cancer in the United States from 1974 to 2013.

Thyroid cancer is a malignant growth of the cells that make up the thyroid glands. It involves several types according to the which cells are malignantly growing and this is identified after a small thyroid tissue (*biopsy*) is examined under the microscope to identify the histological type of the thyroid cancer. As seen in Fig. 4.16, at one extreme, papillary carcinoma has the best prognosis and at the opposite extreme, poorly differentiated types—medullary and anaplastic—are generally the most aggressive with poorest prognoses. The authors found that the increase in incidence of thyroid cancer was almost entirely due to an increase in the incidence of papillary cancer. Within the papillary cancers, most of the increase in this incidence was accounted for by the smallest-sized tumors. Thus, the authors found that 87% of the increase in thyroid cancer incidence over a 30-year period was accounted for by an increase in the smallest-sized papillary cancers, tumors that have the best prognosis. A number of earlier studies have shown a high prevalence of previously unrecognized, asymptomatic small papillary cancers at autopsy. If the increased incidence was due to the availability of more refined diagnostic methods, we would expect to see an increase in the incidence of small tumors, which is exactly what the authors found in their study.

Problems With Mortality Data

Most of our information about deaths comes from death certificates. A death certificate is shown in Fig. 4.17. By international agreement, deaths are coded according to the *underlying cause*. The underlying cause of death is defined as "*the disease or injury which initiated the train of morbid events leading directly or indirectly to death or the circumstances of the accident or violence which produced the fatal injury*."[4] Thus, the death certificate from which Fig. 4.18 is taken would be coded as a death from chronic ischemic heart disease, the underlying cause, which is always found on the lowest line used in part I of item 32 of the certificate. The underlying cause of death therefore "excludes information pertaining to the immediate cause of death, contributory causes, and those causes that intervene between the underlying and immediate causes of death."[5] As pointed out by Savage and coworkers,[6] the total contribution of a given cause of death may not be reflected in the mortality data as generally reported; this may apply to a greater extent in some diseases than in others.

Countries and regions vary greatly in the quality of the data provided on their death certificates. Studies of validity of death certificates compared with hospital and autopsy records generally find higher validity for certain diseases, such as cancers, than for others.

Deaths are coded according to the International Classification of Diseases (ICD), now in its 11th revision (2022). Because coding categories and regulations change from one revision to another, any study of time trends in mortality that spans more than one revision

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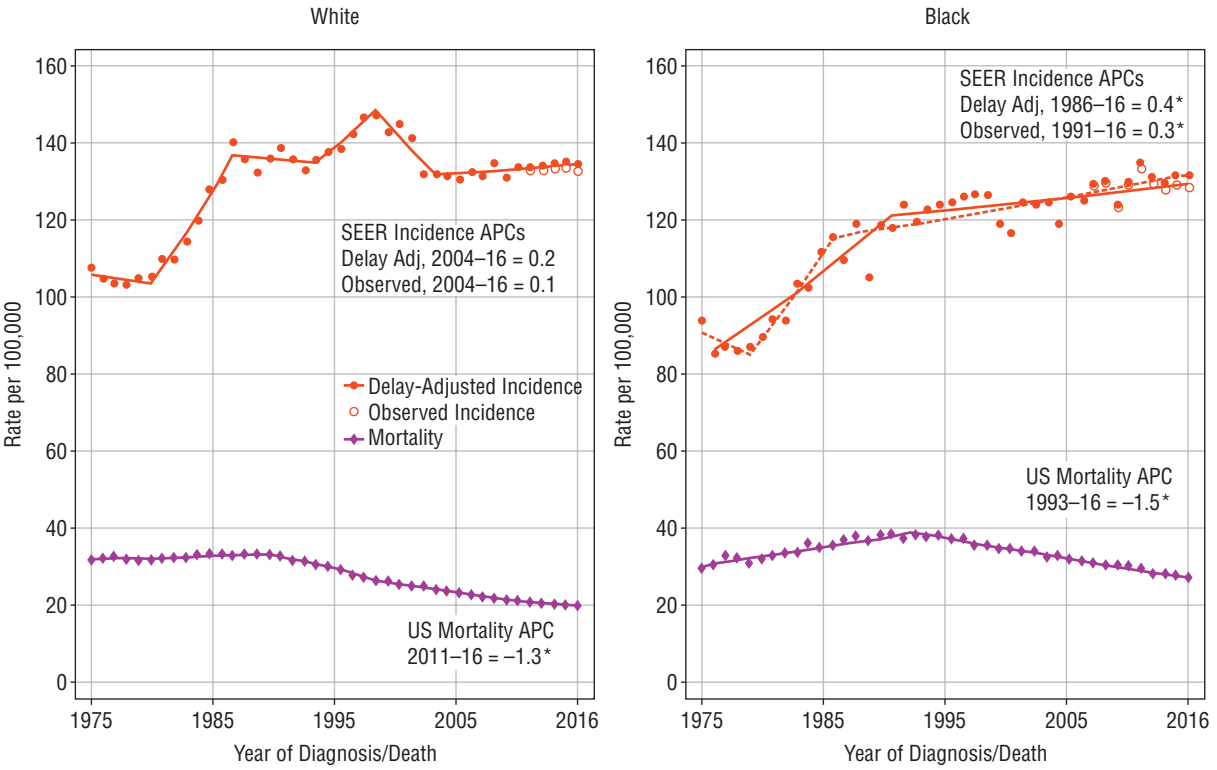


[a]Rates are age-adjusted to the 2000 US Std population (19 age groups - Census P25-1103).
Regression lines and APCs are calculated using the Jointpoint Regression Program Version 4.7. February 2019, National Cancer Institute.
The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.
*The APC is significantly different from zero ($p < 0.05$).

Fig. 4.15 SEER observed incidence, SEER delay adjusted incidence and US death rates[a] cancer of the female breast, by race. *SEER,* Surveillance, Epidemiology, and End Results. (From National Cancer Institute: Surveillance, Epidemiology, and End Results Program. URL: https://seer.cancer.gov/archive/csr/1975_2016/browse_csr.php?sectionSEL=4&pageSEL=sect_04_zfig.01)

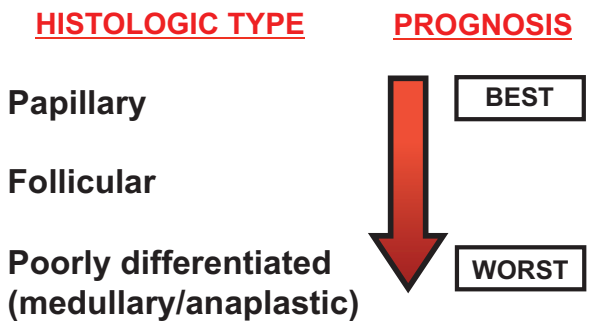
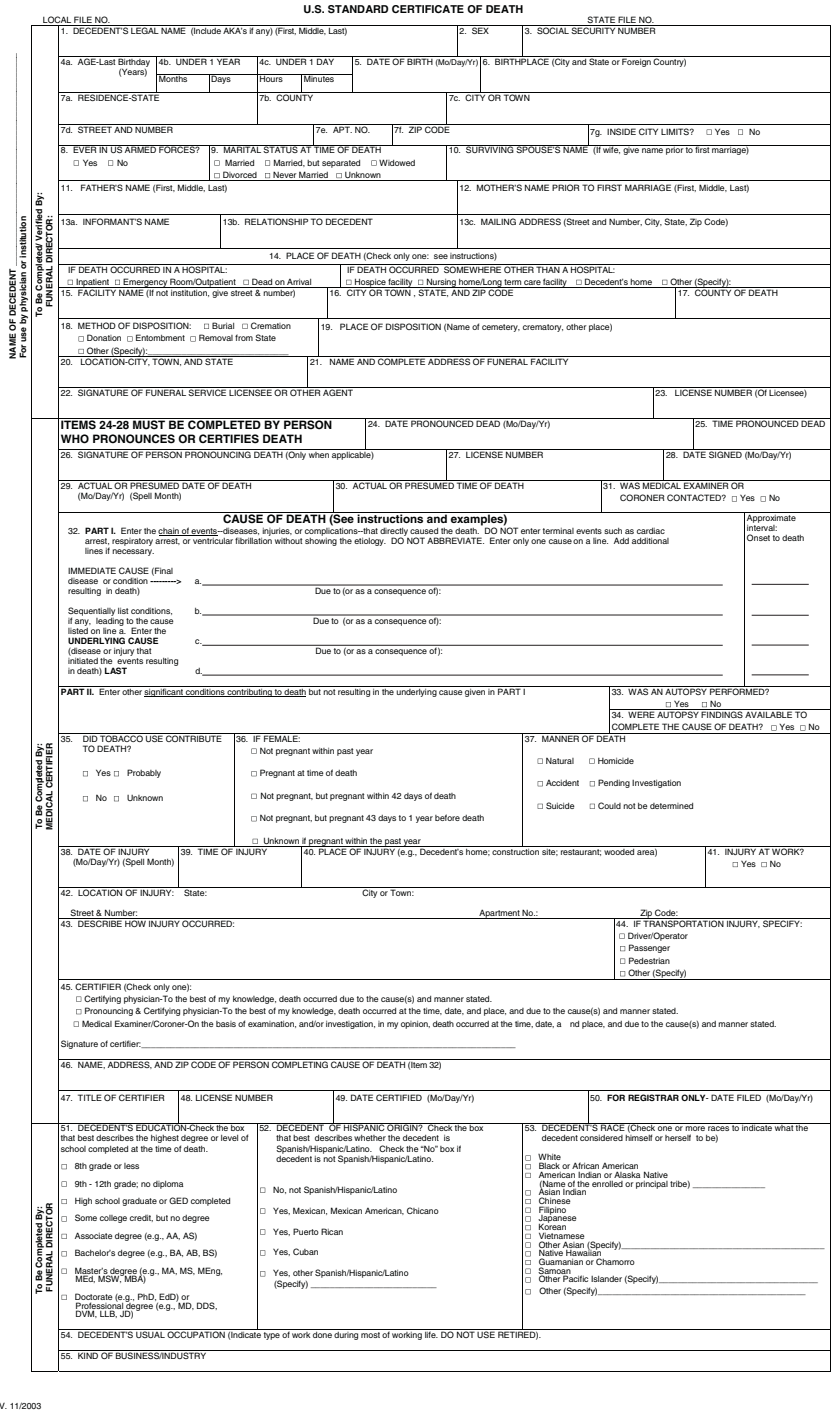


Fig. 4.16 Histologic types of thyroid cancer and their prognoses.

must examine the possibility that observed changes could be due entirely or in part to changes in the ICD. In 1949, mortality rates from diabetes showed a dramatic decline in both men and women (Fig. 4.19). However, any euphoria that these data might have caused was short-lived; analysis of this drop indicated that it occurred at a time of change from the seventh revision to the eighth revision of the ICD. Prior to 1949, the policy was that any death certificate that included mention of diabetes anywhere be coded as a death from diabetes. After 1949, only death certificates on which the underlying cause of death was listed as diabetes were



U.S. STANDARD CERTIFICATE OF DEATH

LOCAL FILE NO. STATE FILE NO.

NAME OF DECEDENT
For use by physician or institution
To Be Completed/ Verified By: FUNERAL DIRECTOR:

1. DECEDENT'S LEGAL NAME (Include AKA's if any) (First, Middle, Last) | 2. SEX | 3. SOCIAL SECURITY NUMBER

4a. AGE-Last Birthday (Years) | 4b. UNDER 1 YEAR Months Days | 4c. UNDER 1 DAY Hours Minutes | 5. DATE OF BIRTH (Mo/Day/Yr) | 6. BIRTHPLACE (City and State or Foreign Country)

7a. RESIDENCE-STATE | 7b. COUNTY | 7c. CITY OR TOWN

7d. STREET AND NUMBER | 7e. APT. NO. | 7f. ZIP CODE | 7g. INSIDE CITY LIMITS? ☐ Yes ☐ No

8. EVER IN US ARMED FORCES? ☐ Yes ☐ No | 9. MARITAL STATUS AT TIME OF DEATH ☐ Married ☐ Married, but separated ☐ Widowed ☐ Divorced ☐ Never Married ☐ Unknown | 10. SURVIVING SPOUSE'S NAME (If wife, give name prior to first marriage)

11. FATHER'S NAME (First, Middle, Last) | 12. MOTHER'S NAME PRIOR TO FIRST MARRIAGE (First, Middle, Last)

13a. INFORMANT'S NAME | 13b. RELATIONSHIP TO DECEDENT | 13c. MAILING ADDRESS (Street and Number, City, State, Zip Code)

14. PLACE OF DEATH (Check only one: see instructions)

IF DEATH OCCURRED IN A HOSPITAL: ☐ Inpatient ☐ Emergency Room/Outpatient ☐ Dead on Arrival
IF DEATH OCCURRED SOMEWHERE OTHER THAN A HOSPITAL: ☐ Hospice facility ☐ Nursing home/Long term care facility ☐ Decedent's home ☐ Other (Specify):

15. FACILITY NAME (If not institution, give street & number) | 16. CITY OR TOWN , STATE, AND ZIP CODE | 17. COUNTY OF DEATH

18. METHOD OF DISPOSITION: ☐ Burial ☐ Cremation ☐ Donation ☐ Entombment ☐ Removal from State ☐ Other (Specify):_____ | 19. PLACE OF DISPOSITION (Name of cemetery, crematory, other place)

20. LOCATION-CITY, TOWN, AND STATE | 21. NAME AND COMPLETE ADDRESS OF FUNERAL FACILITY

22. SIGNATURE OF FUNERAL SERVICE LICENSEE OR OTHER AGENT | 23. LICENSE NUMBER (Of Licensee)

To Be Completed By: MEDICAL CERTIFIER

ITEMS 24-28 MUST BE COMPLETED BY PERSON WHO PRONOUNCES OR CERTIFIES DEATH

24. DATE PRONOUNCED DEAD (Mo/Day/Yr) | 25. TIME PRONOUNCED DEAD

26. SIGNATURE OF PERSON PRONOUNCING DEATH (Only when applicable) | 27. LICENSE NUMBER | 28. DATE SIGNED (Mo/Day/Yr)

29. ACTUAL OR PRESUMED DATE OF DEATH (Mo/Day/Yr) (Spell Month) | 30. ACTUAL OR PRESUMED TIME OF DEATH | 31. WAS MEDICAL EXAMINER OR CORONER CONTACTED? ☐ Yes ☐ No

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death) a._____ Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST** b._____ Due to (or as a consequence of): c._____ Due to (or as a consequence of): d._____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH? ☐ Yes ☐ Probably ☐ No ☐ Unknown

36. IF FEMALE: ☐ Not pregnant within past year ☐ Pregnant at time of death ☐ Not pregnant, but pregnant within 42 days of death ☐ Not pregnant, but pregnant 43 days to 1 year before death ☐ Unknown if pregnant within the past year

37. MANNER OF DEATH ☐ Natural ☐ Homicide ☐ Accident ☐ Pending Investigation ☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month) | 39. TIME OF INJURY | 40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area) | 41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town: Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY: ☐ Driver/Operator ☐ Passenger ☐ Pedestrian ☐ Other (Specify)

45. CERTIFIER (Check only one):
☐ Certifying physician-To the best of my knowledge, death occurred due to the cause(s) and manner stated.
☐ Pronouncing & Certifying physician-To the best of my knowledge, death occurred at the time, date, and place, and due to the cause(s) and manner stated.
☐ Medical Examiner/Coroner-On the basis of examination, and/or investigation, in my opinion, death occurred at the time, date, a nd place, and due to the cause(s) and manner stated.

Signature of certifier:_____

46. NAME, ADDRESS, AND ZIP CODE OF PERSON COMPLETING CAUSE OF DEATH (Item 32)

47. TITLE OF CERTIFIER | 48. LICENSE NUMBER | 49. DATE CERTIFIED (Mo/Day/Yr) | 50. **FOR REGISTRAR ONLY**- DATE FILED (Mo/Day/Yr)

To Be Completed By: FUNERAL DIRECTOR

51. DECEDENT'S EDUCATION-Check the box that best describes the highest degree or level of school completed at the time of death.
☐ 8th grade or less
☐ 9th - 12th grade; no diploma
☐ High school graduate or GED completed
☐ Some college credit, but no degree
☐ Associate degree (e.g., AA, AS)
☐ Bachelor's degree (e.g., BA, AB, BS)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)
☐ Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)

52. DECEDENT OF HISPANIC ORIGIN? Check the box that best describes whether the decedent is Spanish/Hispanic/Latino. Check the "No" box if decedent is not Spanish/Hispanic/Latino.
☐ No, not Spanish/Hispanic/Latino
☐ Yes, Mexican, Mexican American, Chicano
☐ Yes, Puerto Rican
☐ Yes, Cuban
☐ Yes, other Spanish/Hispanic/Latino (Specify) _____

53. DECEDENT'S RACE (Check one or more races to indicate what the decedent considered himself or herself to be)
☐ White
☐ Black or African American
☐ American Indian or Alaska Native (Name of the enrolled or principal tribe) _____
☐ Asian Indian
☐ Chinese
☐ Filipino
☐ Japanese
☐ Korean
☐ Vietnamese
☐ Other Asian (Specify)_____
☐ Native Hawaiian
☐ Guamanian or Chamorro
☐ Samoan
☐ Other Pacific Islander (Specify)_____
☐ Other (Specify)_____

54. DECEDENT'S USUAL OCCUPATION (Indicate type of work done during most of working life. DO NOT USE RETIRED).

55. KIND OF BUSINESS/INDUSTRY

REV. 11/2003

Fig. 4.17 US standard certificate of death. (From Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/data/dvs/death11-03final-acc.pdf. Accessed June 7, 2017.)

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CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

		Approximate interval: Onset to death
IMMEDIATE CAUSE (Final disease or condition ----------> resulting in death)	a. Rupture of myocardium	Mins
	Due to (or as a consequence of):	
Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**	b. Acute myocardial infarction	6 days
	Due to (or as a consequence of):	
	c. Chronic ischemic heart disease	5 years
	Due to (or as a consequence of):	
	d.	

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

Diabetes, Chronic obstructive pulmonary disease, smoking

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

Fig. 4.18 Example of a completed cause-of-death section on a death certificate, including immediate and underlying causes and other significant conditions.

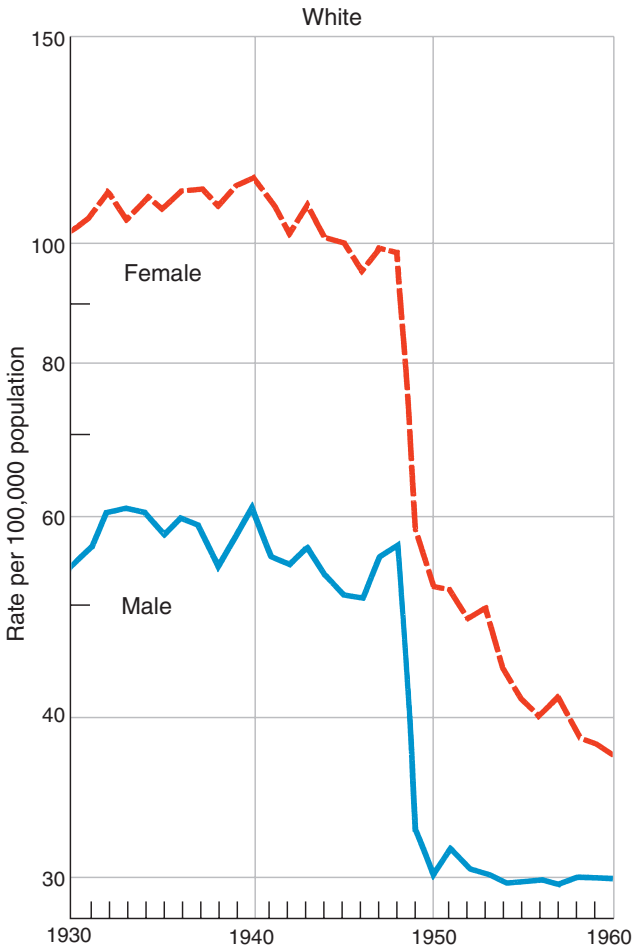

Fig. 4.19 Drop in death rates for diabetes among 55- to 64-year-old men and women, United States, 1930–60, due to changes in International Classification of Diseases coding. (From *US Public Health Service Publication No. 1000, Series 3, No. 1.* Washington, DC: US Government Printing Office; 1964.)

coded as a death from diabetes. Hence, the decline seen in Fig. 4.19 was an artifact of the change in coding. Whenever we see a time trend of an increase or a decrease in mortality, the first question we must ask is, "Is it real?" Specifically, when we look at trends in mortality over time, we must ask whether any changes took place in how death certificates were coded during the period being examined and whether these changes could have contributed to changes observed in mortality during the same period.

Changes in the definition of disease can also have a significant effect on the number of cases of the disease that are reported or that are subsequently classified as meeting the diagnostic criteria for the disease. In early 1993, a new definition of acquired immunodeficiency syndrome (AIDS) was introduced; as shown in Fig. 4.20, this change resulted in a rapid rise in the number of reported cases. With the new definition, even after the initial peak, the number of reported cases remained higher than it had been for several years.

In discussing morbidity in Chapter 3, we said that everyone in the group represented by the denominator must be at risk to enter the group represented by the numerator, and we looked at cervical cancer incidence rates as an example. The same principle regarding numerator and denominator applies to mortality rates. Fig. 4.21 shows a similar set of observations for mortality rates from cervical cancers. Once again, correcting for hysterectomy reduces the number of women in the denominator and thus increases the mortality rate. In a lighter vein, Box 4.2 lists some causes of death that were listed on death certificates early in the 20th century.

COMPARING MORTALITY IN DIFFERENT POPULATIONS

An important use of mortality data is to compare two or more populations, or one population in different time periods. Such populations may differ with regard to many characteristics that affect mortality, of which the age distribution is the most important. In fact, age is the single most important predictor of mortality. Therefore, methods have been developed for comparing mortality in such populations while effectively holding constant characteristics such as age.

Table 4.5 shows data that exemplify this problem. Deaths and death rates by race for residents of the State of Maryland between 1940 and 2019 are given. The data may seem surprising because we would expect rates to have been higher for Black residents, given the problems

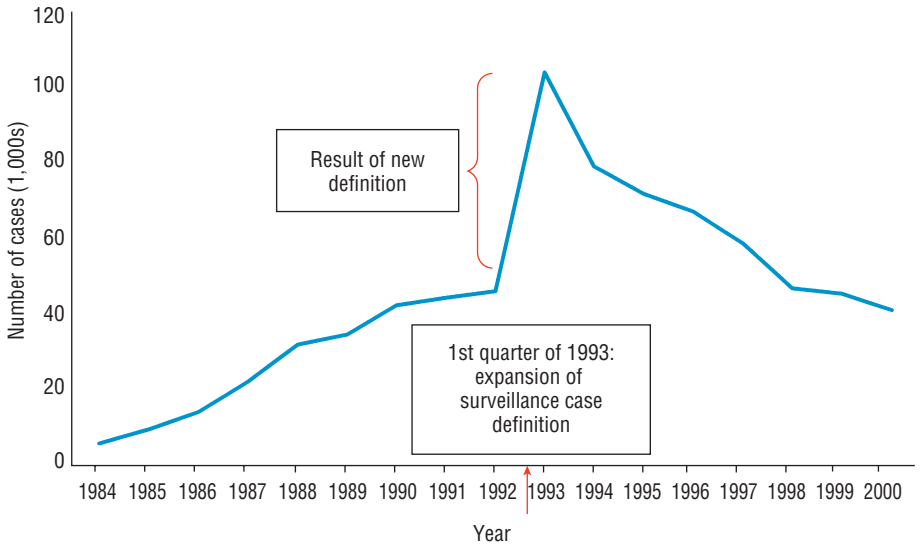

Fig. 4.20 Acquired immunodeficiency syndrome cases by quarter year of report, United States, 1984–2000. (From Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2000. *MMWR*. 2000;49:86; and Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 1993. *MMWR*. 1993;45:68.)

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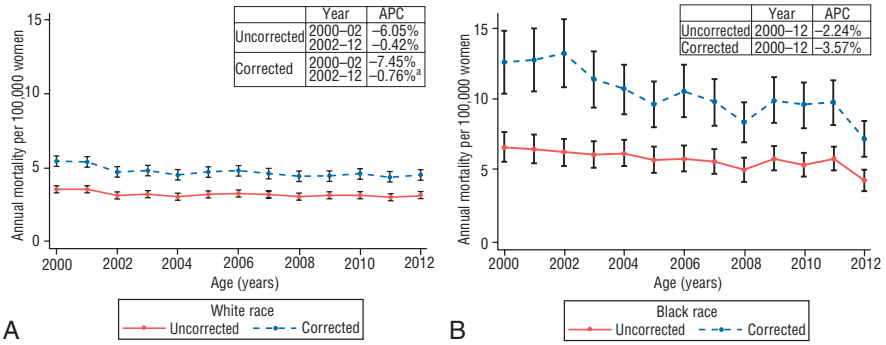

Fig. 4.21 Trends in age-standardized cervical cancer mortality rates, uncorrected and corrected for the prevalence of hysterectomy, from 2000–2012 for (A) White and (B) Black women. *APC,* Annual percentage change. (From Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. *Cancer.* 2017;123:1044–1050.)

BOX 4.2 Some Causes of Death That Were Reported on Death Certificates in the Early 1900s

"Died suddenly without the aid of a physician"
"A mother died in infancy"
"Deceased had never been fatally sick"
"Died suddenly, nothing serious"
"Went to bed feeling well, but woke up dead"

TABLE 4.5 Deaths and Death Rates by Race, Maryland: Selected Years, 1940–2019

	NUMBER OF DEATHS			DEATH RATES[a]		
Year	All Races	White	Black	All Races	White	Black
1940	21,883	16,943	–	11.9	11.1	–
1950	22,450	17,811	–	9.0	8.7	–
1960	27,992	22,447	–	9.0	8.7	–
1970	32,790	26,290	6,448	8.3	8.2	9.2
1980	34,025	26,828	7,056	8.1	8.5	7.3
1990	38,384	28,897	9,172	8.0	8.4	7.6
2000	43,602	31,603	11,349	8.2	8.9	7.5
2010	43,255	30,488	11,761	7.5	8.5	6.6
2011	43,650	30,947	11,645	7.5	8.5	6.5
2012	44,110	31,173	11,884	7.5	8.6	6.5
2013	45,444	31,990	12,358	7.7	8.8	6.7
2014	45,688	31,979	12,559	7.6	8.7	6.7
2015	47,235	32,560	13,434	7.9	8.9	7.1
2016	48,884	33,176	14,113	8.1	9.1	7.4
2017	50,009	33,839	14,507	8.3	9.3	7.5
2018	50,668	33,837	15,034	8.4	9.3	7.8
2019	50,873	33,654	15,290	8.4	9.3	7.9

– Data arc not available
[a] Per 1,000 population
(From Maryland Vital Statistics Annual Report 2019. Maryland Department of Health Vital Statistics Administration. 135. https://health.maryland.gov/vsa/Documents/Reports%20and%20Data/Annual%20Reports/2019Annual.pdf.)

TABLE 4.6 Death Rates by Age and Race, State of Maryland, 2015

	DEATH RATES BY AGE PER 1,000 POPULATION[A]											
Race	All Ages	<1 Year	1–4 Years	5–14 Years	15–24 Years	25–34 Years	35–44 Years	45–54 Years	55–64 Years	65–74 Years	75–84 Years	>85 Years
White	9.95	4.06	0.21	0.11	0.64	1.29	1.73	3.62	7.68	16.45	45.39	138.7
Black	7.35	11.25	0.43	0.18	1.14	1.74	2.23	5.09	11.14	21.55	49.49	124.45

[a]Age-adjusted to the 2000 US population.

From Maryland Vital Statistics Annual Report; 2015. https://health.maryland.gov/vsa/Documents/15annual.pdf. Accessed June 8, 2017. Certain data were provided by the Vital Statistics Administration, Maryland Department of Health, Baltimore, Maryland. The Department disclaims responsibility for any analyses, interpretations, or conclusions.

associated with poorer living conditions and less access to medical care. When we look at Table 4.6, we see the data from Table 4.5 on the left, but now we have added data for each age-specific stratum (layer) of the population. Interestingly, although in each age-specific group, mortality is higher in Black than in White residents, the overall mortality (also called *crude* or *unadjusted mortality*) is higher in White than in Black residents. Why is this so? This is a reflection of the fact that in both White and Black residents, mortality increases markedly in the oldest age groups; older age is the major contributor to mortality. However, the White population in this example is older than the Black population, and in 2015, there were few Black people in the oldest age groups. Thus, in White people, the overall mortality is heavily weighted by high rates in the oldest age groups. The overall (or crude) mortality rate in the White population is increased by the greater number of deaths in the large subgroup of older White people, but the overall mortality rate in the Black population has not increased as much because there are so many fewer deaths in the small number of Black people in the older age groups. Clearly, the crude mortality reflects both differences in the force of mortality and differences in the age composition of the population. Let us look at two approaches for dealing with this problem: direct and indirect age adjustment.

Direct Age Adjustment

Tables 4.7 through 4.9 show a hypothetical example of direct age adjustment. Table 4.7 shows mortality in a population in two different time periods. The mortality rate is considerably higher in the later period. These data are supplemented with age-specific data in Table 4.8.

TABLE 4.7 Hypothetical Example of Direct Age Adjustment: I. Comparison of Total Death Rates in a Population at Two Different Times

EARLY PERIOD			LATER PERIOD		
Population	No. of Deaths	Death Rate per 100,000	Population	No. of Deaths	Death Rate per 100,000
900,000	862	96	900,000	1,130	126

TABLE 4.8 Hypothetical Example of Direct Age Adjustment: II. Comparison of Age-Specific Death Rates in Two Different Time Periods

	EARLY PERIOD			LATER PERIOD		
Age Group (years)	Population	No. of Deaths	Death Rates per 100,000	Population	No. of Deaths	Death Rates per 100,000
All ages	900,000	862	96	900,000	1,130	126
30–49	500,000	60	12	300,000	30	10
50–69	300,000	396	132	400,000	400	100
70+	100,000	406	406	200,000	700	350

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Here, we see three age groups, and age-specific mortality for the later period is lower in each group. How, then, is it possible to account for the higher overall mortality in the later period in this example?

The answer lies in the changing age structure of the population. Mortality is highest in the oldest age groups, and during the later period, the size of the oldest group doubled from 100,000 to 200,000, whereas the number of young people declined substantially, from 500,000 to 300,000. We would like to eliminate this age difference and, in effect, ask: if the age composition of the populations were the same, would there be any differences in mortality between the early period and the later period?

In *direct age adjustment*, a standard population is used in order to eliminate the effects of any differences in age between two or more populations being compared (see Table 4.9). A hypothetical "standard" population is created to which we apply both the age-specific mortality rates from the early period and the age-specific mortality rates from the later period. By applying mortality rates from both periods to a single standard population, we eliminate any possibility that observed differences could be a result of age differences in the population. (In this example, we have created a standard by combining the populations from the early and the later periods, but any population could have been used.)

By applying each age-specific mortality rate to the population in each age group of the standard population, we derive the expected number of deaths that would have occurred had those rates been applied. We can then calculate the total number of deaths expected in the standard population had the age-specific rates of the early period applied and the total number of deaths expected in the standard population had the age-specific rates of the later period applied. Dividing each of these two total expected numbers of deaths by the total standard population, we can calculate an expected mortality rate in the standard population if it had had the mortality experience of the early period and the expected mortality rate for the standard population if it had had the mortality experience for the later period. These are called *age-adjusted rates*, and they appropriately reflect the decline seen in the age-specific rates. Differences in age-composition of the population are no longer a factor.

In this example the rates have been adjusted for age, but adjustment can also be carried out for any characteristic of interest such as sex, socioeconomic status, or race, and techniques are also available to adjust for multiple variables simultaneously.

Although age-adjusted rates can be very useful in making comparisons, the first step in examining and analyzing comparative mortality data should always be to carefully examine the *age-specific* rates for any interesting differences or changes. These differences may be hidden by the *age-adjusted* rates and may be lost if we proceed immediately to age adjustment without first examining the age-specific rates.

TABLE 4.9 Hypothetical Example of Direct Age Adjustment: III. Carrying Out an Age Adjustment Using the Total of the Two Populations as the Standard

Age Group (years)	Standard Population	"Early" Age-Specific Mortality Rates per 100,000	Expected No. of Deaths Using "Early" Rates	"Later" Age-Specific Mortality Rates per 100,000	Expected No. of Deaths Using "Later" Rates
All ages	1,800,000				
30–49	800,000	12	96	10	80
50–69	700,000	132	924	100	700
70+	300,000	406	1,218	350	1,050
Total no. of deaths expected in the standard population:		2,238		1,830	
Age-adjusted rates:		$\text{"Early"} = \frac{2{,}238}{1{,}800{,}000} = 124.3$		$\text{"Later"} = \frac{1{,}830}{1{,}800{,}000} = 101.7$	

Age-adjusted rates are *hypothetical* because they involve applying actual age-specific rates to a hypothetical standard population. They do not reflect the true mortality risk of a "real" population because the numerical value of an age-adjusted death rate depends on the standard population used. Selection of such a population is somewhat arbitrary because there is no "correct" standard population, but it is generally accepted that the "standard" should not be markedly different from the populations that are being compared with regard to age or whatever the variable is for which the adjustment is being made. In the United States, for more than 50 years, the 1940 US population was regularly used as the standard population for age adjustment for most purposes, but in recent years, this population was increasingly considered outdated and incompatible with the older age structure of the US population. Beginning with 1999 mortality statistics, the US population in the year 2000 replaced the 1940 population as the standard population for adjustment.

The change in standard population to the year 2000 US population has had some significant effects, as illustrated with a comparison of cause-specific mortality rates using data through 1995.[7] These include increases in age-adjusted mortality rates that were observed for causes in which risk increases significantly with age. For example, age-adjusted death from cerebrovascular diseases (stroke) is 26.7 deaths per 100,000 using the 1940 standard, but it is 63.9 per 100,000 using the 2000 standard. Cancer mortality increased using the 2000 population standard compared to when an earlier population was used as a standard because more people are surviving into older ages, when many of the leading types of cancer are more common. Rates for heart disease, chronic obstructive lung disease, diabetes, kidney disease, and Alzheimer disease were similarly affected because age-specific death rates for all these conditions are higher in older age groups.

Age-adjusted rates of cancer are higher in Black people compared to White people in the United States, but the differential between Black and White people is less with the 2000 population standard than with the earlier standard population. Thus, the change to the year 2000 US population as the standard complicates comparisons of age-adjusted rates before and after 1999, because many of the rates before 1999 were calculated using the 1940 standard population. However, the rates from 1999 forward are being calculated using the year 2000 population as the new standard.

In summary, the goal of direct adjustment is to compare rates in at least two different populations when we wish to eliminate the possible effect of a given factor, such as age, on the rates we are comparing. It is important to keep in mind that adjusted rates are not "real" rates in the populations being compared, because they depend on the choice of the standard population used in carrying out the adjustment. Nevertheless, direct adjustment is a very useful tool for making such comparisons and in fact, comparison of rates in different populations almost always utilizes direct adjustment, such as adjustment for age. Note that adjustment is based on replacing each population with a common set of weights (the standard population) in order to estimate weighted averages—that is, the adjusted rates.

Indirect Age Adjustment (Standardized Mortality Ratios)

Indirect age adjustment is often used when numbers of deaths for each age-specific stratum are not available. It is also used to study mortality in an occupationally exposed population: Do people who work in a certain industry, such as mining or construction, have a higher mortality than people of the same age in the general population? Is an additional risk associated with that occupation?

To answer the question of whether a population of workers has a higher mortality than we would expect in a similar population that is not engaged in the occupation being observed, the age-specific rates for a known population, such as all men of the same age, are applied to each age group in the population of interest. This will yield the number of deaths expected in each age group in the population of interest, if this population had had the mortality experience of the known population. Thus, for each age group, the number of deaths *expected* is calculated, and these numbers are totaled. The numbers of deaths that were actually *observed* in that population are also calculated and totaled. The ratio of the total number of deaths actually observed to the total number of deaths expected, if the population of interest had the mortality experience of the known population, is then calculated. This ratio is called the *standardized mortality ratio* (*SMR*).

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TABLE 4.10 Hypothetical Computation of a Standardized Mortality Ratio (SMR) for Disease X for White Workers Ages 20–59 Years, 2023

	Estimated Population for White Workers	Death Rate (per 100,000) for Disease X in Males in the General Population	Expected Deaths From Disease X in White Workers If They Had Same Risk as General Population	Observed Deaths From Disease in White Workers
Age (years)	1	2	3 = 1 × 2	4
20–24	62,253	8.9	5.5	5
25–29	72,732	12.7	9.3	15
30–34	68,500	18.1	12.4	17
35–44	136,525	30.6	41.7	93
45–54	90,304	53.4	48.2	169
55–59	30,149	71.8	21.7	107
Totals	460,463		138.8	406

$$\text{SMR (for 20- to 59-year-olds)} = \frac{406}{138.8} \times 100 = 292$$

The SMR is defined as follows:

$$\text{SMR} = \frac{\text{Observed no. of deaths per year}}{\text{Expected no. of deaths per year}}$$

Let us look at the example in Table 4.10. In a hypothetical population of 460,463 White male workers, 406 deaths from disease X occurred in 2023. The question we are interested in is whether this mortality experience from disease X is greater than, less than, or about the same as that expected in White men of the same ages in the general population (most of whom are not included in this classification of workers). To help address this question, we may calculate the expected number of deaths for White workers in each age group by applying the known age-specific mortality rate from the general population to the number of workers in each age group. By doing so, we ask, "How many deaths would we expect in these White workers if they had the same mortality experience as White men in the same age group in the general population?" These data are listed in column 3. Column 4 shows the number of deaths observed in the workers.

The SMR is calculated by totaling the observed number of deaths (406) and dividing it by the expected number of deaths (138.8), which yields a result of 2.92. Multiplication by 100 is often done to yield results without decimals. If this were done in this case, the SMR would be 292. An SMR of 100 indicates that the observed number of deaths is the same as the expected number of deaths. An SMR greater than 100 indicates that the observed number of deaths exceeds the expected number, and an SMR less than 100 indicates that the observed number of deaths is less than the expected number.

The Cohort Effect

Table 4.11 shows age-specific obesity prevalence (%) from 1971 to 2006 in the United States using data from the National Center for Health Statistics. (For this discussion, we will ignore the data for age groups 2 to 19 years, since childhood obesity is a somewhat different phenomenon.) If, for example, we then read *down* the column in the table (the data for a given National Health and Nutrition Examination Survey [NHANES] cycle) for 1971–1975, it appears that obesity prevalence peaks in the age group 55 to 59 years and then declines with advancing age. Such a view of the data, by year, is called a *cross-sectional view*.

Actually, however, the picture of obesity prevalence is somewhat different (Table 4.12). A person who was 20 to 24 years of age in 1971 was 25 to 29 years of age in 1976. In other words, persons who were born in a certain year are moving through time together. We can now examine the obesity prevalence over time of the same cohort (i.e., a group of people who share the

TABLE 4.11 Age-Period Contingency Table for Obesity Prevalence by Age (Rows) and Period (Columns) in the United States, 1971–2006 (N = 91,755)

	NHANES I	NHANES II	NHANES III, Phase 1	NHANES III, Phase 2	NHANES 99–00	NHANES 01–02	NHANES 03–04	NHANES 05–06
	1971–75	1976–80	1988–91	1991–94	1999–2000	2001–02	2003–04	2005–06
2–4	3.1	3.25	3.48	4.34	7.02	6.29	8.72	8.54
5–9	5.48	7.17	8.75	13.12	17.45	16.92	20.22	16.25
10–14	6.88	7.9	8.93	13.57	18.97	18.72	22.85	21.81
15–19	6.64	5.5	8.31	13.55	18.03	17.8	19.94	18.43
20–24	6.08	7.14	9.87	13.81	20.59	26.67	26.59	24.98
25–29	10.34	10.49	11.97	18.74	27.69	26.55	26.47	35.9
30–34	13.64	13.49	18.02	20.07	31.64	24.82	30.19	36.6
35–39	14.34	14.73	17.24	23.3	29.08	30.19	36.54	33.3
40–44	16.76	15.82	19.27	24.63	32.68	32.85	39.68	42.69
45–49	15.26	18.05	18.85	30.75	31.93	35.83	35.79	38.5
50–54	17.18	17.46	22.37	35.42	40.55	31.69	39.32	38.73
55–59	19.5	19.62	26.55	32.46	35.7	38	38.62	46.9
60–64	18.68	17.57	20.82	30.67	41.37	44.28	34.49	42.67
65–69	16.83	18.51	21.26	27.79	41.23	35.43	38	40.64
70–74	17.15	16.31	18.68	25.03	29.34	34.87	32.48	31.45

NHANES, National Health and Nutrition Examination Survey.
From Keyes KM, Utz RL, Robinson W, Li G. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971–2006. *Soc Sci Med.* 2010;70(7):1100–1108.

same experience), born in the same 5-year period. Looking at persons who were 20 to 24 years of age in the 1971–1975 cycle and following them over time, as indicated by the bold black boxes in the table, it is apparent that obesity prevalence for this *cohort* has been increasing throughout the years and did not decline later on, as we have seen in the cross-sectional view of the data. When we examine changes in prevalence over time, we should always ask whether any apparent changes that are observed could be the result of such a cohort effect.

Interpreting Observed Changes in Mortality

If we find a difference in mortality over time or between populations—either an increase or a decrease—it may be an artifact or it may be real. If it is an artifact, the artifact could result from problems with either the numerator or the denominator (Table 4.13). However, if we conclude that the change is real, what could be the possible explanation? Some possibilities are seen in Box 4.3.

OTHER MEASURES OF THE IMPACT OF DISEASE

Quality of Life

Most diseases have a major impact on the afflicted individuals above and beyond mortality. Diseases that may not be lethal may be associated with considerable physical and emotional suffering, resulting from disability associated with the illness. It is therefore important to consider the total impact of a disease as measured by its effect on a person's quality of life, even though such measures are not, in fact, measures of disease occurrence. For example, it is possible to examine the extent to which patients with arthritis are compromised by the illness in carrying out activities of daily living. In addition, regulatory authorities such as the US Food and Drug Administration review and evaluate quality of life as part of the patient-reported outcome measures that can be used to support claims of improving patients' quality of life in approved drug labels.

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TABLE 4.12 Age-Period Contingency Table for Obesity Prevalence by Age (Rows) and Period (Columns) in the United States, 1971–2006 (N = 91,755)

Age (years)	NHANES I 1971–75	NHANES II 1976–80	NHANES III, Phase 1 1988–91	NHANES III, Phase II 1991–94	NHANES 99–00 1999–2000	NHANES 01–02 2001–02	NHANES 03–04 2003–04	NHANES 05–06 2005–06
2–4	3.1	3.25	3.48	4.34	7.02	6.29	8.72	8.54
5–9	5.48	7.17	8.75	13.12	17.45	16.92	20.22	16.25
10–14	6.88	7.9	8.93	13.57	18.97	18.72	22.85	21.81
15–19	6.64	5.5	8.31	13.55	18.03	17.8	19.94	18.43
20–24	**6.08**	7.14	9.87	13.81	20.59	26.67	26.59	24.98
25–29	10.34	**10.49**	11.97	18.74	27.69	26.55	26.47	35.9
30–34	13.64	13.49	**18.02**	20.07	31.64	24.82	30.19	36.6
35–39	14.34	14.73	17.24	**23.3**	29.08	30.19	36.54	33.3
40–44	16.76	15.82	19.27	24.63	**32.68**	32.85	39.68	42.69
45–49	15.26	18.05	18.85	30.75	31.93	**35.83**	35.79	38.5
50–54	17.18	17.46	22.37	35.42	40.55	31.69	**39.32**	38.73
55–59	19.5	19.62	26.55	32.46	35.7	38	38.62	**46.9**
60–64	18.68	17.57	20.82	30.67	41.37	44.28	34.49	42.67
65–69	16.83	18.51	21.26	27.79	41.23	35.43	38	40.64
70–74	17.15	16.31	18.68	25.03	29.34	34.87	32.48	31.45

Bold black boxes denote persons who were 20 to 24 years of age during the 1971–1975 cycle and were followed over time, forming a cohort.
NHANES, National Health and Nutrition Examination Survey.

From Keyes KM, Utz RL, Robinson W, Li G. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971–2006. *Soc Sci Med.* 2010;70(7):1100–1108.

TABLE 4.13 Possible Explanations of Trends or Differences in Mortality: I. Artifactual

1. Numerator	Errors in diagnosis Errors in age Changes in coding rules Changes in classification
2. Denominator	Errors in counting population Errors in classifying by demographic characteristics (e.g., age, race, sex) Differences in percentages of populations at risk

BOX 4.3 Possible Explanations of Trends or Differences in Mortality: II. Real

Change in diagnostic modalities or management strategies
Change in survivorship without change in incidence
Change in incidence
Change in age composition of the population(s)
A combination of the above factors

Although considerable controversy exists about which quality-of-life measures are most appropriate and valid, there is general agreement that such measures can be reasonably used to plan short-term treatment programs for groups of patients. Such patients can be evaluated over a period of months to determine the effects of the treatment on their self-reported quality of life. Quality-of-life measures have also been used for establishing priorities in situations of scarce health care resources. Although prioritizing health care resources is often primarily based on mortality data, quality of life must also be taken into account for this purpose, because many diseases are chronic and non–life-threatening but may be associated with many years of disability, having both physical and mental health consequences. Patients may place different weights on different quality-of-life measures depending on differences in

their occupations and other activities, personalities, cultural backgrounds, education, and moral and ethical values. As a result, measuring quality of life and developing valid indices that are useful for obtaining comparative data in different patients and in different populations remain major challenges.

Projecting the Future Burden of Disease

An interesting and valuable use of current data to predict the future impact of disease was a comprehensive assessment of current mortality and disability from diseases, injuries, and risk factors for all regions of the world in 1990, which was projected to the year 2020. The study, titled the Global Burden of Disease, attempted to quantify not only deaths but also the impact of premature death and disability on a population and to combine these into a single index to express the overall "burden of disease."[8] The index that was developed for this study is the disability-adjusted life year (DALY), which is the number of years of life lost to premature death and years lived with a disability of specified severity and duration. Thus, a DALY is 1 lost year of healthy life.

The results showed that 5 of the 10 leading causes of disability in 1990 were psychiatric conditions; psychiatric and neurologic conditions accounted for 28% of all years lived with disability of known severity and duration, compared with 1.4% of all deaths and 1.1% of years of life lost. Fig. 4.22 shows the burden of disease among the world's poorest billion people vs. high-income regions.[9,10] Again, the importance of ischemic heart disease in high-income countries and lower respiratory tract infections in low-income countries is dramatically evident.

In 2019 the disease burden was not equitably distributed. As seen in Table 4.14, the top 20 causes of disease burden were responsible for 57.2% of all DALYs. Five of them primarily affect children younger than 5 years of age. Three of the top ten (ischemic heart disease, stroke, and depression) are chronic conditions. This table shows the value of using a measure such as DALYs to assess the burden of disease, a measure that is not limited to either morbidity or mortality but is weighted by both.

With the aging of the population worldwide and advances in economic development, particularly in low- and middle-income countries, an "epidemiologic transition" is taking place so that, by 2020, noncommunicable diseases accounted for 70% of all deaths in developing countries. As projected in Fig. 4.23, by 2020,

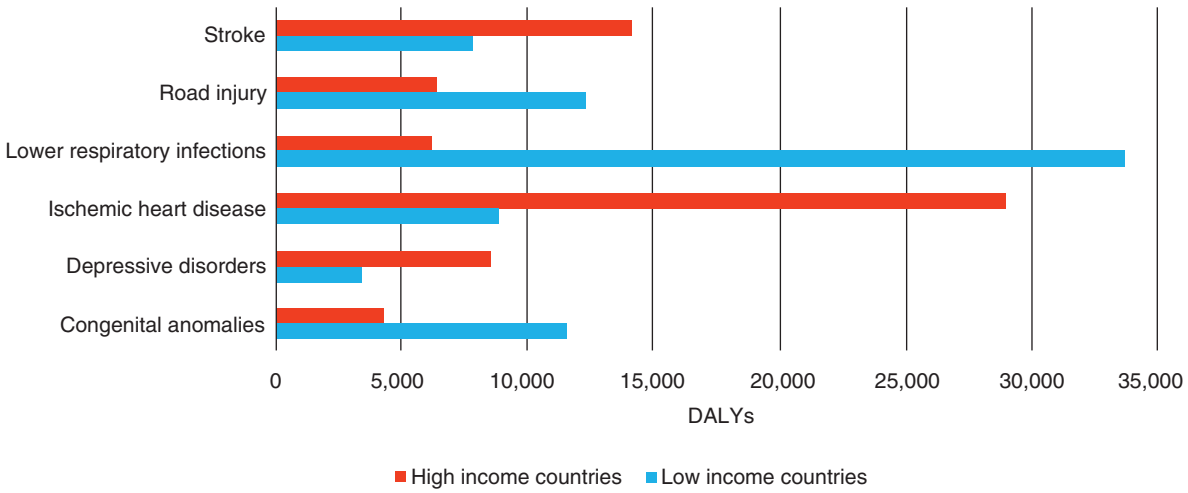

Fig. 4.22 Selected causes of disease burden by low- versus high-income countries, 2015. *DALYs,* Disability-adjusted life years. (From Global Health Estimates 2015. *Disease Burden by Cause, Age, Sex, by Country and by Region, 2000–2015.* Geneva, Switzerland: World Health Organization; 2016.)

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TABLE 4.14 Global Health Estimates 2019: 20 Leading Causes of DALYs Globally, 2019

Rank	Cause	DALYs (000s)	% DALYs	DALYs per 100,000 Population
0	**All Causes**	**2,531,710**	**100.0**	**32,844**
1	Neonatal conditions	201,821	8.0	2,618
2	Ischemic heart disease	180,847	7.1	2,346
3	Stroke	139,429	5.5	1,809
4	Lower respiratory infections	105,652	4.2	1,371
5	Diarrheal diseases	79,311	3.1	1,029
6	Road injury	79116	3.1	1,026
7	Chronic obstructive pulmonary disease	73,981	2.9	960
8	Diabetes mellitus	70,411	2.8	913
9	Tuberculosis	66,024	2.6	857
10	Congenital anomalies	51,797	2.0	672
11	Back and neck pain	46532	1.8	604
12	Depressive disorders	46,359	1.8	601
13	Cirrhosis of the liver	42,798	1.7	555
14	Trachea, bronchus, lung cancers	41,378	1.6	537
15	Kidney diseases	40,571	1.6	526
16	HIV/AIDS	40,147	1.6	521
17	Other hearing loss	39,477	1.6	512
18	Falls	38,216	1.5	496
19	Malaria	33,398	1.3	433
20	Uncorrected refractive errors	31,981	1.3	415

AIDS, Acquired immunodeficiency syndrome; *DALYs,* disability-adjusted life years; *HIV,* human immunodeficiency virus.
Data from Global Health Estimates 2019: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva, World Health Organization; 2020. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates

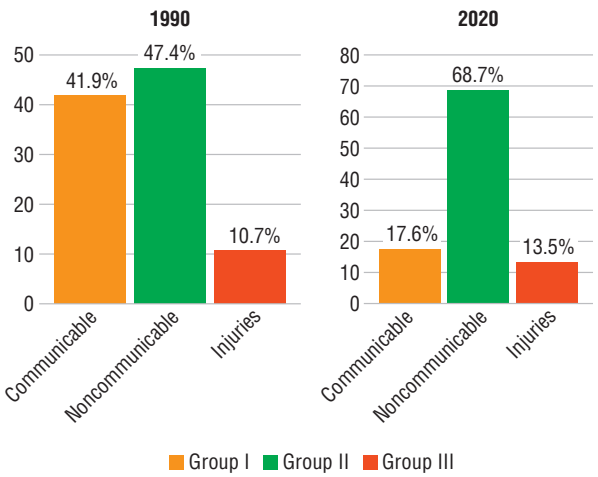

Fig. 4.23 The "epidemiologic transition": distribution of deaths from communicable and noncommunicable causes in developing countries, 1990 and projected into 2020. (From Murray CJL, Lopez AD. *The Global Burden of Disease: a Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020.* Cambridge: Harvard University Press on behalf of the World Health Organization and the World Bank; 1996.)

the disease burden due to communicable diseases, maternal and perinatal conditions, and nutritional deficiencies decreased dramatically. The burden due to noncommunicable diseases (group II) is expected to increase sharply, as will the burden from injuries (group III). The burden of disease attributable to tobacco exceeded that caused by any single disease—clearly a strong call for public health action. Although there is no universal agreement on the methodology or applicability of a single measure of disease burden such as the DALY, this study is an excellent demonstration of an attempt at worldwide surveillance designed to develop such a measure to permit valid regional comparisons and future projections so that appropriate interventions can be developed.

CONCLUSION

Chapters 3 and 4 have reviewed important approaches to quantitatively measuring and expressing human morbidity and mortality. The concepts reviewed in these chapters may at first seem overwhelming but, as

we shall see in later chapters, they are critical to understanding how epidemiology helps us to elucidate the measurement of disease risk, the determination of disease causation, and the evaluation of the effectiveness of intervening to modify the disease process.

In Chapter 5, we will turn to questions about the numerators of morbidity rates: how do we identify those people who have a disease and distinguish them from those who do not, and how do we evaluate the quality of the diagnostic and screening tests that are used to separate these individuals and populations? A discussion of the use of screening tests in public health programs is presented in Chapter 18.

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REVIEW QUESTIONS FOR CHAPTER 4

Questions 1 and 2 are based on the information given below:

In an Asian country with a population of 6 million people, 60,000 deaths occurred during the year ending December 31, 2010. These included 30,000 deaths from cholera in 100,000 people who were sick with cholera.

1. *What was the cause-specific mortality rate from cholera in 2010?* _____

2. *What was the case-fatality from cholera in 2010?* _____

3. *Age-adjusted death rates are used to:*
- **a.** Correct death rates for errors in the statement of age
- **b.** Determine the actual number of deaths that occurred in specific age groups in a population
- **c.** Correct death rates for missing age information
- **d.** Compare deaths in persons of the same age group
- **e.** Eliminate the effects of differences in the age distributions of populations in comparing death rates

4. *The mortality rate from disease X in city A is 75/100,000 in persons 65 to 69 years old. The mortality rate from the same disease in city B is 150/100,000 in persons 65 to 69 years old. The inference that disease X is two times more prevalent in persons 65 to 69 years old in city B than it is in persons 65 to 69 years old in city A is:*
- **a.** Correct
- **b.** Incorrect, because of failure to distinguish between prevalence and mortality
- **c.** Incorrect, because of failure to adjust for differences in age distributions
- **d.** Incorrect, because of failure to distinguish between period and point prevalence
- **e.** Incorrect, because a proportion is used when a rate is required to support the inference

5. *The incidence rate of a disease is five times greater in women than in men, but the prevalence rates show no sex difference. The best explanation is that:*
- **a.** The crude all-cause mortality rate is greater in women
- **b.** The case-fatality from this disease is greater in women

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c. The case-fatality from this disease is lower in women
d. The duration of this disease is shorter in men
e. Risk factors for the disease are more common in women

6. *For a disease such as pancreatic cancer, which is highly fatal and of short duration:*
a. Incidence rates and mortality rates will be similar
b. Mortality rates will be much higher than incidence rates
c. Incidence rates will be much higher than mortality rates
d. Incidence rates will be unrelated to mortality rates
e. None of the above

7. *In 1990, there were 4,500 deaths due to lung diseases in miners aged 20 to 64 years. The expected number of deaths in this occupational group, based on age-specific death rates from lung diseases in all males aged 20 to 64 years, was 1,800 during 1990. What was the standardized mortality ratio (SMR) for lung diseases in miners?* _____

Question 8 is based on the information given below:

Annual Cancer Deaths in White Male Workers in Two Industries

	INDUSTRY A		INDUSTRY B	
Cancer Site	**No. of Deaths**	**% of All Cancer Deaths**	**No. of Deaths**	**% of All Cancer Deaths**
Respiratory system	180	33	248	45
Digestive system	160	29	160	29
Genitourinary	80	15	82	15
All other sites	130	23	60	11
Totals	550	100	550	100

Based on the preceding information, it was concluded that workers in industry B are at higher risk of death from respiratory system cancer than workers in industry A. (Assume that the age distributions of the workers in the two industries are nearly identical.)

8. *Which of the following statements is true?*
a. The conclusion reached is correct
b. The conclusion reached may be incorrect because proportionate mortality rates were used when age-specific mortality rates were needed
c. The conclusion reached may be incorrect because there was no comparison group
d. The conclusion reached may be incorrect because proportionate mortality was used when cause-specific mortality rates were needed
e. None of the above

9. *A program manager from an international health funding agency needs to identify regions that would benefit from an intervention aimed at reducing premature disability. The program manager asks a health care consultant to develop a proposal using an index that would help her make this decision. Which of the following would best serve this purpose?*
a. Case-fatality
b. Crude mortality rate
c. Disability-adjusted life-years
d. Standardized mortality ratio

10. *The following are standardized mortality ratios (SMRs) for lung cancer in England:*

	STANDARDIZED MORTALITY RATIOS	
Occupation	**1949–60**	**1968–79**
Carpenters	209	135
Bricklayers	142	118

Based on these SMRs alone, it is possible to conclude that:
a. The number of deaths from lung cancer in carpenters in 1949–60 was greater than the number of deaths from lung cancer in bricklayers during the same period
b. The proportionate mortality from lung cancer in bricklayers in 1949–60 was greater than the proportionate mortality from lung cancer in the same occupational group in 1968–79
c. The age-adjusted rate of death from lung cancer in bricklayers was greater in 1949–60 than it was in 1968–79
d. The rate of death from lung cancer in carpenters in 1968–79 was greater than would have been expected for a group of men of similar ages in all occupations
e. The proportionate mortality rate from lung cancer in carpenters in 1968–79 was 1.35 times

greater than would have been expected for a group of men of similar ages in all occupations

Questions 11, 12, and 13 are based on the information given below:

Numbers of People and Deaths from Disease Z by Age Group in Communities X and Y

	COMMUNITY X		COMMUNITY Y	
Age Group	No. of People	No. of Deaths From Disease Z	No. of People	No. of Deaths From Disease Z
Young	8,000	69	5,000	48
Old	11,000	115	3,000	60

Calculate the age-adjusted death rate for disease Z in communities X and Y by the direct method, using the total of both communities as the standard population.

11. *The age-adjusted death rate from disease Z for community X is: _____*

12. *The proportionate mortality from disease Z for community Y is: _____*

a. 9.6/1,000
b. 13.5/1,000
c. 20.0/1,000
d. 10.8/1,000
e. None of the above

13. *Which of the following statements regarding direct adjustment is TRUE?*

a. The age-adjusted mortality rate of community X is still higher than the mortality rate of community Y, as compared to the crude mortality rate
b. Age-adjusted mortality rates for community X should be used to make decisions regarding allocation of funding for hospital care of the dying in community X
c. For direct age-adjustment, the weight for a given age category is the percentage of deaths for that age group
d. For direct age-adjustment, the weight for a given age category is the number of individuals in the standard population for that age group
e. The difference in the adjusted mortality rates between community X and community Y is always attributable to differences in age composition between the two populations

14. *Surveillance data indicate that the prevalence of chronic liver disease in the United States increased 104% between the years 1990 and 2008. While chronic liver disease occurs in persons of all ages, the highest mortality rate occurs in people 65 years old or older. The United States has proportionately more people 65 years or older than Country X. What would happen if crude mortality rates in the United States were age standardized to the population of Country X in order to compare the risk of dying of chronic liver disease in the two populations?*

a. The age-standardized mortality rate for the United States would be less than the crude mortality rate for the United States
b. The age-standardized mortality rate for the United States would be greater than the crude mortality rate for the United States
c. The age-standardized mortality rate for the United States would be the same as the crude mortality rate for the United States
d. The age-standardized mortality rate for the United States cannot be used for this comparison
e. The age-standardized mortality rate for the United States would be the same as the proportionate mortality rate

15. *Among workers in a fish processing plant, 30% of all deaths were due to myocardial infarction. Among workers in a brewery, 10% of all deaths were due to myocardial infarction. Investigators concluded that workers in the fish processing plant had a greater risk of death due to myocardial infarction than workers in the brewery. This conclusion:*

a. Is correct
b. May be incorrect because it is based on proportionate mortality
c. May be incorrect because it assumes the same case fatality for myocardial infarction in both work sites
d. May be incorrect because consumed fish oil is protective against death due to myocardial infarction
e. May be incorrect because the prevalence of myocardial infarction in the two groups is not known

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5

Assessing the Validity and Reliability of Diagnostic and Screening Tests

A normal individual is a person who has not been sufficiently examined.

—Anonymous

LEARNING OBJECTIVES

- To define the validity and reliability of screening and diagnostic tests.
- To compare measures of validity, including sensitivity and specificity.
- To illustrate the use of multiple tests (sequential and simultaneous testing).
- To introduce positive and negative predictive value.
- To address measures of reliability, including percent agreement and kappa.

To understand how a disease is transmitted and develops and to provide appropriate and effective health care, it is necessary to distinguish between people in the population who have the disease and those who do not. This is an important challenge, both clinically, where patient care is the issue, and in the public health arena, where secondary prevention programs involving early disease detection through screening and interventions are fielded and where etiologic studies are conducted to provide a basis for primary prevention, if possible. Thus, the quality of screening and diagnostic tests is a critical issue. Regardless of whether the test is a physical examination, a chest x-ray, an electrocardiogram, or a blood or urine assay, the same issue arises: *How good is the test in correctly identifying populations of people with and without the disease in question?* This chapter addresses the question of how we assess the quality of newly available screening and diagnostic tests to make reasonable decisions about their use and interpretation. Such decisions can be made for a variety of goals, such as public health screening programs, clinical diagnosis, initiating treatment, or modifying clinical management of patients.

BIOLOGIC VARIATION OF HUMAN POPULATIONS

In using a test to distinguish between individuals with normal and abnormal results, it is important to understand how characteristics are distributed in human populations.

Fig. 5.1 shows the distribution of newly reported confirmed cases of hepatitis C virus infection in Massachusetts for 2009. We can see that there are two peaks of hepatitis C virus infection cases among young adults and middle-aged persons. This type of distribution, in which there are two peaks, is called a *bimodal curve*. The bimodal distribution permits the identification of increased rates of *new cases* among these two distinct age groups, which could be related to different reasons. In this situation, there has been a dramatic increase in hepatitis among injection drug users, a practice associated with sharing of injection equipment that led to this bimodal distribution.

In general, however, most human characteristics are not distributed bimodally. Fig. 5.2 shows the distribution of low-density lipoprotein cholesterol (LDL-C)

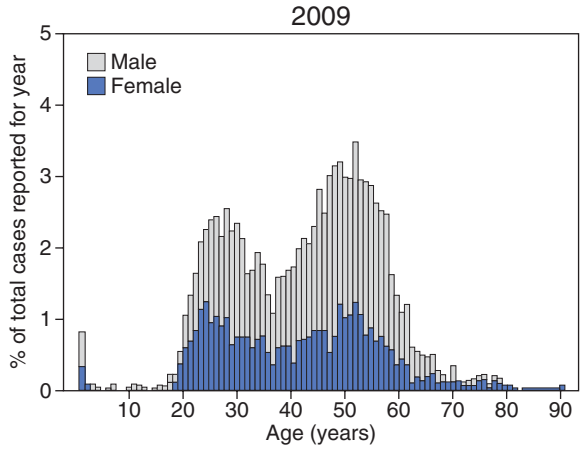
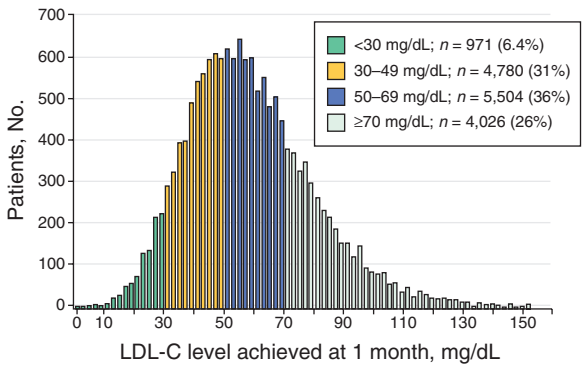


Fig. 5.1 Distribution of newly reported confirmed cases of hepatitis C virus infection in Massachusetts for 2009. (Modified from Centers for Disease Control and Prevention. Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002–2009. *MMWR Morb Mortal Wkly Rep*. 2011; 60:537–541.)



The median LDL-C level was 56 mg/dL (interquartile range, 43–70 mg/dL).
to convert LDL-C to millimoles per liter, multiply by 0.0259.

Fig. 5.2 Distribution of achieved calculated low-density lipoprotein cholesterol *(LDL-C)* level at 1 month among patients who did not have a primary efficacy or prespecified safety event prior to the sample. (Data from Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT trial. *JAMA Cardiol*. 2017;2:547–555.)

concentration in participants of a clinical trial to study the safety of intensively reducing LDL-C as compared with less intensive LDL-C level lowering in patients after acute coronary syndrome. In this figure, there is no bimodal curve; what we see is a *unimodal curve*—a single peak. Therefore, if we want to separate those in the group who achieved a safe low level of LDL-C, a cutoff level of LDL-C must be set below which people are labeled as achieving the "safe low level" and above which they are not labeled as such. This study shows that there is no obvious level of LDL-C that should be a treatment target. Although we could choose a cutoff based on statistical considerations, as the authors in this study showed, we would ideally like to choose a cutoff on the basis of some biologic information—that is, we would want to know that an intensive LDL-C lowering strategy below the chosen cutoff level is associated with increased risk of subsequent treatment side effects (e.g., adverse muscle, hepatobiliary, and neurocognitive events) or disease complications (e.g., hemorrhagic stroke, heart failure, cancer, and noncardiovascular death). Unfortunately, for many human characteristics, we do not have such information to serve as a guide in setting this level.

In either distribution—unimodal or bimodal—it is usually easy to distinguish between the extreme values of abnormal and normal. With either type of curve, however, uncertainty remains about cases that fall into the gray zone.

VALIDITY OF SCREENING TESTS

The *validity* of a test is defined as its ability to correctly distinguish between who has a disease and who does not. Validity has two components: sensitivity and specificity. The *sensitivity* of the test is defined as the ability of the test to correctly identify those who *have* the disease. The *specificity* of the test is defined as the ability of the test to correctly identify those who *do not have* the disease.

Tests With Dichotomous Results (Positive or Negative)

Suppose we have a hypothetical population of 1,000 people, of whom 100 have a certain disease and 900 do not. A test is available that gives either positive or negative results. We want to use this test to distinguish persons who have the disease from those who do not. The results obtained by applying the test to this population of 1,000 people are shown in Table 5.1.

How good was the test? First, how good was the test in correctly identifying those who had the disease? Table 5.1 indicates that of the 100 people with the disease, 80 were correctly identified as "positive" by the test,

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TABLE 5.1 Calculation of the Sensitivity and Specificity of Screening Examinations

Example: Assume a population of 1,000 people, of whom 100 have the disease and 900 do not have the disease. A screening test is used to identify the 100 people who have the disease.

	TRUE CHARACTERISTICS IN THE POPULATION		
Results of Screening	**Have the Disease**	**Do Not Have the Disease**	**Totals**
Positive	80	100	180
Negative	20	800	820
Totals	100	900	1,000

Sensitivity: $\frac{80}{100} = 80\%$

Specificity: $\frac{800}{900} = 89\%$

and a positive identification was missed in 20. Thus, the *sensitivity* of the test, which is defined as the proportion of diseased people who were correctly identified as "positive" by the test, is 80/100, or 80%.

Second, how good was the test in correctly identifying those who did not have the disease? Looking again at Table 5.1, of the 900 people who did not have the disease, the test correctly identified 800 as "negative." The *specificity* of the test, which is defined as the proportion of non-diseased people who are correctly identified as "negative" by the test, is therefore 800/900, or 89%.

To calculate the sensitivity and specificity of a test, we must know who "really" has the disease and who "does not" from a source other than the test we are using. We are, in fact, comparing our test results with some gold standard—an external source of "truth" regarding the disease status of each individual in the population. Sometimes this truth may be the result of another test that has been in use, and sometimes it is the result of a more definitive, and often more invasive, test (e.g., tumor biopsy, cardiac catheterization, or tissue biopsy). However, in real life, when we use a test to identify diseased and non-diseased persons in a population, we clearly do not know who has the disease and who does not. (If this were already established, testing would be pointless.) But to quantitatively assess the sensitivity and specificity of a test, we must have another source of truth with which to compare the test results.

Table 5.2 compares the results of a dichotomous test (results are unambiguously either positive or negative) with the actual disease status. Ideally, we would like all of the tested subjects to fall into the two cells shown in the upper left and lower right on the table: people with the disease who are correctly called "positive" by the test *(true positives)* and people without the disease who are correctly called "negative" by the test *(true negatives)*. Unfortunately, such is rarely if ever the case. Some people who do not have the disease are erroneously called "positive" by the test *(false positives)*, and some people with the disease are erroneously called "negative" *(false negatives)*.

Why are these issues important? When we conduct a screening program, we often have a large group of people who screened positive, including both people

TABLE 5.2 Comparison of the Results of a Dichotomous Test With Disease Status

Test Results	TRUE CHARACTERISTICS IN THE POPULATION: Have the Disease	Do Not Have the Disease
Positive	**True Positive (TP):** Have the disease and test positive	**False Positive (FP):** Do not have the disease but test positive
Negative	**False Negative (FN):** Have the disease but test negative	**True Negative (TN):** Do not have the disease and test negative

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Specificity} = \frac{TN}{TN + FP}$$

who really have the disease *(true positives)* and people who do not have the disease *(false positives)*. The issue of *false positives* is important because all people who screened positive are brought back for more sophisticated and more expensive tests or perhaps undergo an invasive procedure that is not necessary. Of the several problems that result, the first is a burden on the health care system. Another is the anxiety and worry induced in persons who have been told that they have tested positive. Considerable evidence indicates that many people who are labeled "positive" by a screening test never have that label completely erased, even if the results of a subsequent evaluation are negative. For example, children labeled "positive" in a screening program for heart disease may be handled as fragile by parents and school personnel even after being told that subsequent more definitive tests were negative. In addition, such individuals may be limited in regard to employment and insurability by erroneous interpretation of positive screening test results, even if subsequent tests fail to substantiate any positive finding.

During the COVID-19 pandemic, the issue of false positives was underscored as it related to which test is able to correctly identify individuals who are infected with SARS-CoV-2. Reverse transcription polymerase chain reaction (RT-PCR) testing is considered the gold standard, but it is expensive and results are only available after a relatively long time. The swift identification of individuals with SARS-CoV-2 infection is key to initiate isolation, explore early therapeutic options for the patient, conduct contact tracing and testing, and control transmission of disease. The emergence of a rapid antigen test resulted in a less expensive and faster test to identify individuals with SARS-Cov-2 infection, which could be used for frequent testing of asymptomatic employees in the workplace. However, there were concerns

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about its validity, i.e., its ability to correctly identify individuals with the infection. Gans et al.[1] studied 903,408 rapid antigen tests in 537 workplaces in Canada as a voluntary, twice-weekly screening for asymptomatic employees. There were 1322 positive results (0.15%), for which 1103 had RT-PCR information. False-positive test results, defined by positive rapid antigen test and negative RT-PCR test, were found in 462 test results (42%). While this can initially raise concerns, the authors further examined the lot number of these tests and found that 60% of the false positives occurred in two workplaces with same lot number. This example shows the practical importance of validity and false-positive identification in distinguishing test limitations, manufacturing issues, or implementation challenges.

Why is the problem of *false negatives* also important? If a person has the disease but is erroneously informed that the test result is negative, and if the disease is a serious one for which effective intervention is available, the problem is indeed critical. For example, if the disease is a type of cancer that is curable only in its early stages, a false-negative result could represent a virtual death sentence. Thus, the importance of false-negative results depends on the nature and severity of the disease being screened for, the effectiveness of available intervention measures, and whether the effectiveness is greater if the intervention is administered early in the natural history of the disease.

Tests of Continuous Variables

So far, we have discussed a test with only two possible results: positive or negative. But we often test for a continuous variable, such as blood pressure or blood glucose level, for which there is no obvious "positive" or "negative" result. A decision must therefore be made in establishing a cutoff level above which a test result is considered positive and below which a result is considered negative. Let's consider the diagrams shown in Fig. 5.3.

Fig. 5.3A shows a population of 20 diabetic patients and 20 nondiabetic patients who are being screened using a blood sugar test whose scale is shown along the vertical axis from high to low. The diabetic patients are represented by blue circles and the nondiabetic patients by red circles. We see that although blood sugar levels tend to be higher in diabetic than in nondiabetic patients, no level clearly separates the two groups; there is some overlap of diabetic and nondiabetic patients at every blood sugar level. Nevertheless, we must select a cutoff point so that those whose results fall above the cutoff can be called "positive," and can be called back for further testing, and those whose results fall below that point are called "negative," and are not called back for further testing.

Suppose a relatively high cutoff level is chosen (see Fig. 5.3B). Clearly, many of the diabetic patients will not be identified as positive; on the other hand, most of the nondiabetic patients will be correctly identified as negative. If these results are distributed on a 2×2 table, the sensitivity of the test using this cutoff level will be 25% (5/20) and the specificity will be 90% (18/20). So, most of the diabetic patients will not be detected, but most of the nondiabetic patients will be correctly classified.

What if a low cutoff level is chosen (see Fig. 5.3C)? Very few diabetic patients would be misdiagnosed. What, then, is the problem? A large proportion of the nondiabetic patients are now identified as positive by the test. As seen in the 2×2 table, the sensitivity is now 85% (17/20), but the specificity is only 30% (6/20).

The difficulty is that in the real world, no vertical line separates the diabetic and nondiabetic patients, and they are indeed mixed together (see Fig. 5.3D); in fact, they are not even distinguishable by red or blue circles (see Fig. 5.3E). So, if a high cutoff level is used (see Fig. 5.3F), all those with results below the line will be assured they do not have the disease and will not be followed further; if the low cutoff is used (see Fig. 5.3G), all those with results above the line will be brought back for further testing.

Fig. 5.4A shows actual data from a historical report regarding the distribution of blood sugar levels in diabetic and nondiabetic patients. Suppose we were to screen this population. If we decide to set the cutoff level so that we identify all of the diabetic patients (100% sensitivity), we could set the level at 80 mg/dL (see Fig. 5.4B). The problem is, however, that in so doing we will also call many of the nondiabetic patients positive—that is, the specificity will be very low. On the other hand, if we set the level at 200 mg/dL (see Fig. 5.4C) so that we call all the nondiabetic patients negative (100% specificity), we now miss many of the true diabetic patients because the sensitivity will be very low. Thus, there is a trade-off between sensitivity and specificity: if we increase the sensitivity by lowering the cutoff level, we decrease the specificity; if we increase the specificity by raising the cutoff level, we decrease the

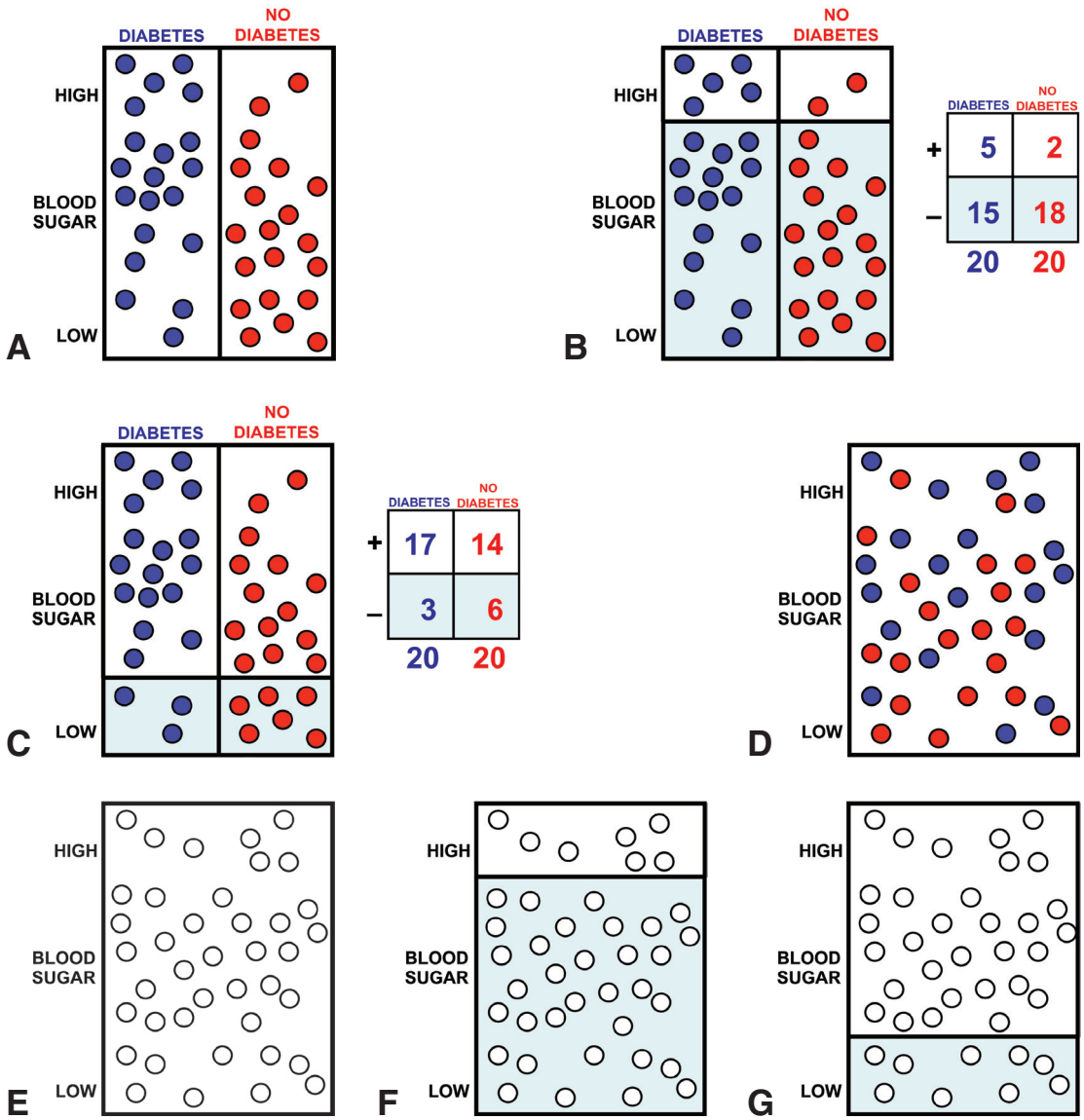

Fig. 5.3 **(A** to **G)** The effects of choosing different cutoff levels to define a positive test result when screening for diabetes using a continuous marker, blood sugar, in a hypothetical population. (See discussion in the text under the subheading "Tests of Continuous Variables" on page 100.)

sensitivity. To quote an unknown sage: "There is no such thing as a free lunch."

The dilemma involved in deciding whether to set a high cutoff or a low cutoff rests in the problem of the false positives and the false negatives that result from the testing. It is important to remember that in screening we end up with groups classified only on the basis of the results of their screening tests, either positive or negative. We have no information regarding their true disease status, which, of course, is the reason for carrying out the screening. In effect, the results of the screening test yield not four groups, as seen in Fig. 5.5, but rather two groups: one group of people who tested positive and one group who tested negative. Those who

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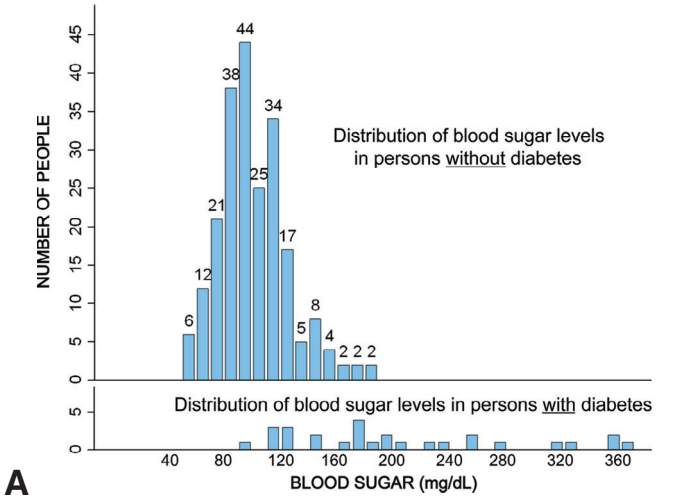

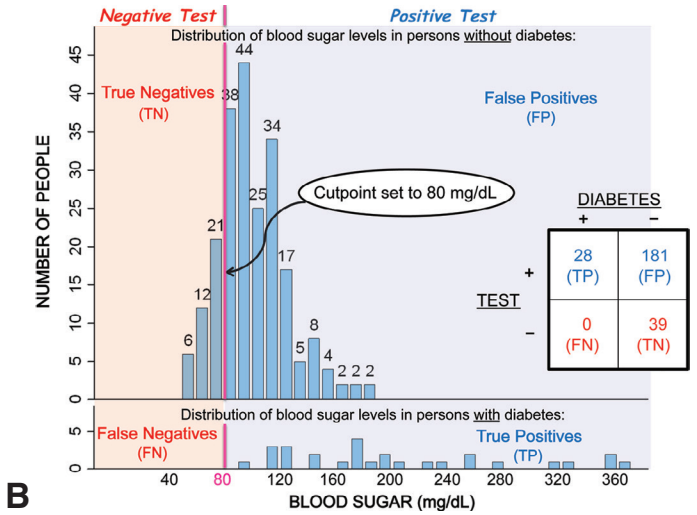

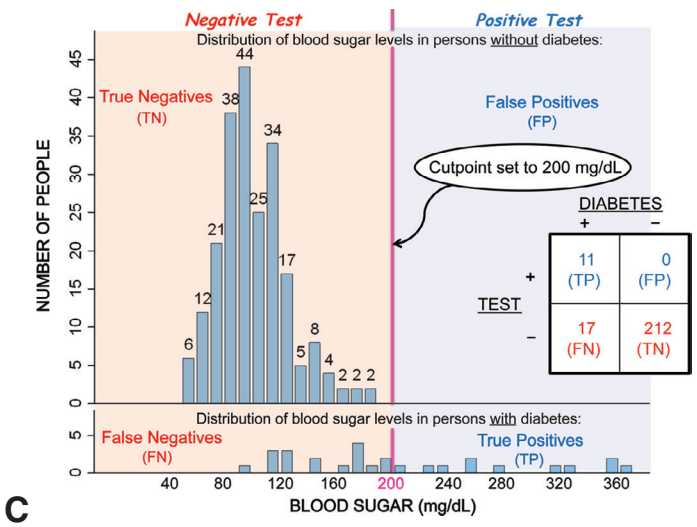

Fig. 5.4 **(A)** Distribution of blood sugar levels in hospital patients with diabetes and without diabetes. (The number of people with diabetes is shown for each specific blood sugar level in the *[upper]* distribution for persons *without* diabetes. Because of limited space, the number of people for each specific level of blood sugar is not shown in the *[lower]* distribution for persons *with* diabetes.) **(B)** and **(C)** show two different blood sugar cutoff points that were used in the study to define diabetes. Data from the graphs are presented to the right of each graph in a 2 × 2 table. (B) When a blood sugar cutoff point of ≥80 mg/dL is used to define diabetes in this population, sensitivity of the screening test is 100%, but specificity is low. (C) When a blood sugar cutoff point of ≥200 mg/dL is used to define diabetes in this population, sensitivity of the screening test is low, but specificity is 100%. (See explanation in the text under the subheading "Tests of Continuous Variables" on page 100.) *FN*, False negatives; *FP*, false positives; *TN*, true negatives; *TP*, true positives. (Modified from Blumberg M. Evaluating health screening procedures. *Oper Res*. 1957;5:351–360.)

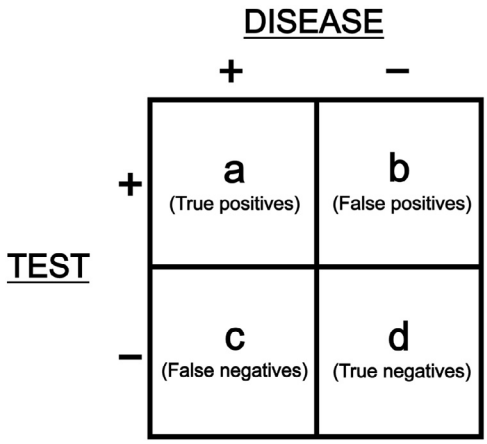

Fig. 5.5 Diagram showing four possible groups resulting from screening with a dichotomous test.

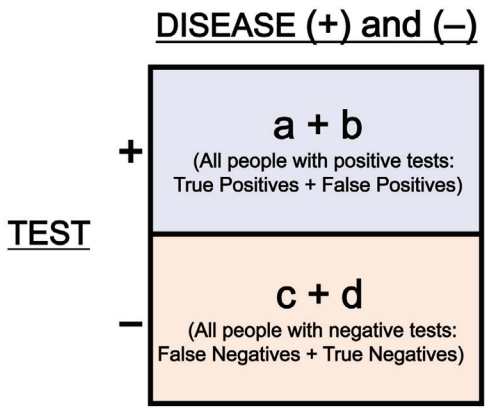

Fig. 5.6 Diagram showing the two groups of people resulting from screening with a dichotomous screening test: all people with positive test results and all people with negative test results.

tested positive will be notified of their test result and will be asked to return for additional examinations. The other group, who tested negative, will be notified that their test result was negative and will therefore not be asked to return for further testing (Fig. 5.6).

The choice of a high or a low cutoff level for screening therefore depends on the importance we attach to false positives and false negatives. False positives are associated with costs—emotional and financial—as well as with the difficulty of "delabeling" a person who tests positive and is later found not to have the disease. In addition, false-positive results may pose a major burden to the health care system, in that a large group of people need to be brought back for a retest, when only a few of them may have the disease. Those with false-negative results, on the other hand, will be told they do not have the disease and will not be followed, so a serious disease might possibly be missed at an early treatable stage. Thus the choice of cutoff level relates to the relative importance of false positivity and false negativity for the disease in question.

USE OF MULTIPLE TESTS

Often more than one screening test may be applied in the same individuals to detect an illness—either sequentially (one after another) or simultaneously (both conducted at the same time). The results of these approaches are described in this section.

Sequential (Two-Stage) Testing

In sequential (or two-stage) screening, a less expensive, less invasive, or less uncomfortable test is generally performed first, and those who screen positive are recalled for further testing with a more expensive, more invasive, or more uncomfortable test, which may have greater sensitivity and specificity. It is hoped that bringing back for further testing only those who screen positive will reduce the problem of false positives.

Consider the hypothetical example in Fig. 5.7A, in which a population is screened for diabetes using a test with a sensitivity of 70% and a specificity of 80%. How are the data shown in this table obtained? The disease prevalence in this population is given as 5%, so that in the population of 10,000, 500 persons have the disease. With a sensitivity of 70%, the test will correctly identify 350 of the 500 people who have the disease. With a specificity of 80%, the test will correctly identify as nondiabetic 7,600 of the 9,500 people who are free of diabetes; however, 1,900 of these 9,500 will have positive results. Thus, a total of 2,250 people will test positive and will be brought back for a second test. (Remember that in real life we do not have the vertical line separating diabetic and nondiabetic patients, and we do not know that only 350 of the 2,250 have diabetes.)

Now those 2,250 people are brought back and screened using a second test (such as a glucose tolerance test), which, for purposes of this example, is assumed to have a sensitivity of 90% and a specificity of 90%. Fig. 5.7B shows test 1 together with test 2, which deals only with the 2,250 people who tested positive in

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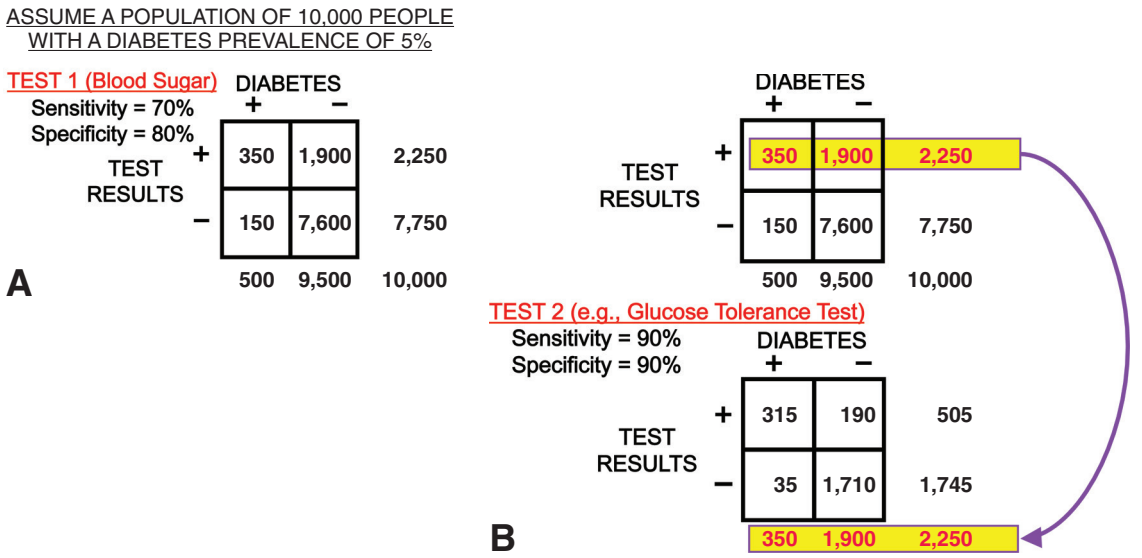

Fig. 5.7 Hypothetical example of a two-stage screening program. **(A)** Findings using test 1 in a population of 10,000 people. **(B)** Findings using test 2 in participants who tested positive using test 1. (See explanation in the text under the subheading "Sequential (Two-Stage) Testing" on page 103.)

the first screening test and have been brought back for second-stage screening.

Since 350 people (of the 2,250) have the disease and the second test has a sensitivity of 90%, 315 of those 350 will be correctly identified as positive. Because 1,900 (of the 2,250) do not have diabetes and the test specificity is 90%, 1,710 of the 1,900 will be correctly identified as negative and 190 will be false positives.

We are now able to calculate the *net sensitivity* and the *net specificity* of using both tests in sequence. After finishing both tests, 315 people of the total 500 people with diabetes in this population of 10,000 will have been correctly called positive: 315/500 = 63% *net sensitivity* (which can also be calculated by multiplying the sensitivity of the first test times the sensitivity of the second test; i.e., $0.70 \times 0.90 = 0.63$). Thus, there is a loss in net sensitivity by using both tests sequentially. To calculate *net specificity*, note that 7,600 people of the 9,500 in this population who do not have diabetes were correctly called negative in the first-stage screening and were not tested further; an additional 1,710 of those 9,500 nondiabetic patients were correctly called negative in the second-stage screening. Thus a total of 7,600 + 1,710 of the 9,500 nondiabetic patients were correctly called negative: 9,310/9,500 = 98% *net specificity*. Thus use of both tests in sequence has resulted in a gain in *net specificity*.

Simultaneous Testing

Let's now turn to the use of simultaneous tests. We assume that in a population of 1,000 people, the prevalence of a disease is 20%. Therefore 200 people have the disease, but we do not know who they are. In order to identify the 200 people who have this disease, we screen this population of 1,000 using two tests for this disease, test A and test B, at the same time. We assume that the sensitivity and specificity of the two tests are as follows:

Test A	Test B
Sensitivity = 80%	Sensitivity = 90%
Specificity = 60%	Specificity = 90%

Net Sensitivity Using Two Simultaneous Tests

The first question we ask is, "What is the *net sensitivity* using test A and test B *simultaneously*?" To be considered positive and therefore included in the numerator for net sensitivity for two tests used simultaneously, a person must be identified as positive by test A, test B, or both tests.

TABLE 5.3 Results of Screening With Test A

Results of Screening	POPULATION: Disease	POPULATION: No Disease
Positive	160	320
Negative	40	480
Totals	200	800
	Sensitivity = 80%	Specificity = 60%

To calculate net sensitivity, let's first consider the results of screening with test A whose sensitivity is 80%: of the 200 people who have the disease, 160 test positive (Table 5.3). In Fig. 5.8A, the oval represents the 200 people who have the disease. In Fig. 5.8B the pink circle within the oval represents the 160 who test positive with test A. These 160 are the true positives using test A.

Consider next the results of screening with test B whose sensitivity is 90% (Table 5.4). Of the 200 people who have the disease, 180 test positive by test B. In Fig. 5.8C, the oval again represents the 200 people who have the disease. The blue circle within the oval represents the 180 who test positive with test B. These 180 are the true positives using test B.

In order to calculate the numerator for net sensitivity, we cannot just add the number of persons who tested positive using test A to those who tested positive using test B because some people tested positive on both tests. These people are shown in lavender by the overlapping area of the two circles, and we do not want to count them twice (see Fig. 5.8D). How do we determine how many people tested positive on both tests?

Test A has a sensitivity of 80% and thus identifies as positive 80% of the 200 who have the disease (160 people). Test B has a sensitivity of 90%. Therefore, it identifies as positive 90% of the same 160 people who are identified by test A (144 people). Thus when tests A and B are used simultaneously, 144 people are identified as positive by both tests (see Fig. 5.8E).

Recall that test A correctly identified 160 people with the disease as positive. Because 144 of them were identified by both tests, 160 − 144, or 16 people, were correctly identified *only* by test A.

Test B correctly identified 180 of the 200 people with the disease as positive. Because 144 of them were identified by both tests, 180 − 144, or 36 people, were correctly identified *only* by test B. Thus as seen in Fig. 5.8F, using tests A and B simultaneously,

$$\text{Net sensitivity} = \frac{16+144+36}{200} = \frac{196}{200} = 98\%$$

Net Specificity Using Two Simultaneous Tests

The next question is, "What is the *net specificity* using test A and test B *simultaneously*?" To be included in the numerator for net specificity for two tests used simultaneously, a person must be identified as *negative by both tests*. In order to calculate the numerator for net specificity, we therefore need to determine how many people had negative results on both tests. How do we do this?

Test A has a specificity of 60% and thus correctly identifies 60% of the 800 who do not have the disease (480 people; Table 5.5). In Fig. 5.9A, the oval represents the 800 people who do not have the disease. The green circle within the oval in Fig. 5.9B represents the 480 people who test negative with test A. These are the true negatives using test A.

Test B has a specificity of 90% and thus identifies as negative 90% of the 800 people who do not have the disease (720 people; Table 5.6 and the yellow circle in Fig. 5.9C). However, to be called negative in simultaneous tests, only people who test negative on both tests are considered to have had negative results (see Fig. 5.9D). These people are shown in light green by the overlapping area of the two circles. Test B also identifies as negative 90% of the same 480 people identified as negative by test A (432 people). Thus, as shown by the overlapping circles, when tests A and B are used simultaneously, 432 people are identified as negative by both tests (see Fig. 5.9E). Thus when tests A and B are used simultaneously (see Fig. 5.9F),

$$\text{Net specificity} = \frac{432}{800} = 54\%$$

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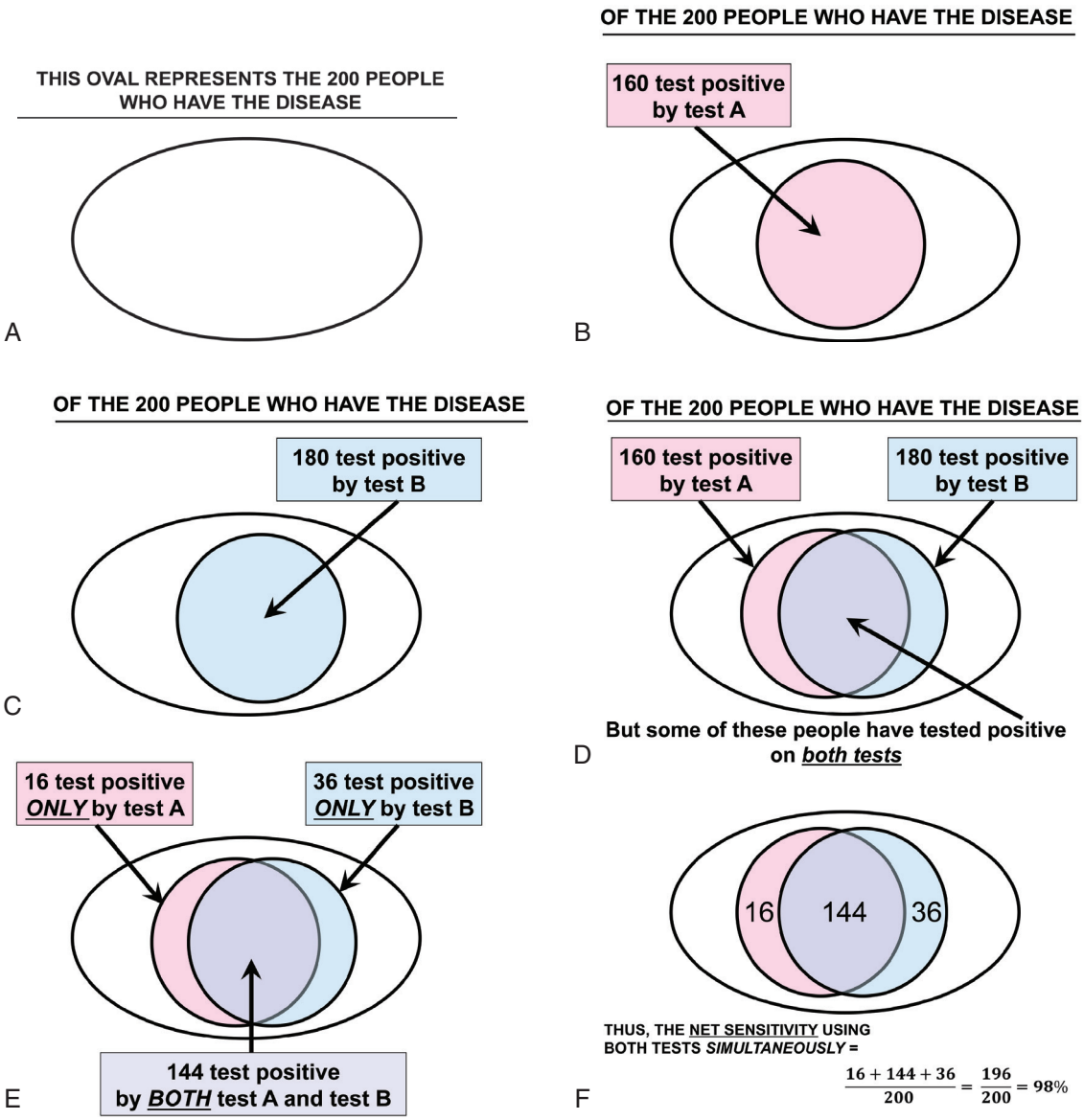

Fig. 5.8 **(A** to **F)** Net sensitivity: hypothetical example of simultaneous testing. (See explanation in the text under the subheading "Net Sensitivity Using Two Simultaneous Tests" on page 104.)

Therefore, when two simultaneous tests are used, there is a net gain in sensitivity (from 80% using test A and 90% using test B to 98% using both tests simultaneously). However, there is a net loss in specificity (net specificity = 54%) compared with using either test alone (specificity of 60% using test A and 90% using test B).

Comparison of Simultaneous and Sequential Testing

In a clinical setting, multiple tests are often used simultaneously. For example, a patient admitted to a hospital may have an array of tests performed at the time of admission. When multiple tests are used simultaneously to detect a specific disease, the individual is generally

TABLE 5.4 Results of Screening With Test B

Results of Screening	POPULATION: Disease	POPULATION: No Disease
Positive	**180**	80
Negative	20	720
Totals	200	800
	Sensitivity = 90%	Specificity = 90%

TABLE 5.5 Results of Screening With Test A

Results of Screening	POPULATION: Disease	POPULATION: No Disease
Positive	160	320
Negative	40	**480**
Totals	200	800
	Sensitivity = 80%	Specificity = 60%

considered to have tested "positive" if they have a positive result on *any* one or more of the tests. The individual is considered to have tested "negative" if they test negative on *all* of the tests. The effects of such a testing approach on sensitivity and specificity differ from those that result from sequential testing. In sequential testing, when we retest those who tested positive on the first test, there is a loss in net sensitivity and a gain in net specificity. In simultaneous testing, because an individual who tests positive on *any* one or multiple tests is considered positive, there is a gain in net sensitivity. However, to be considered negative, a person would have to test negative on *all* the tests performed. As a result, there is a loss in net specificity.

In summary, as we have seen previously, when two sequential tests are used and those who test positive by the first test are brought in for the second test, there is a net loss in sensitivity, but a net gain in specificity, compared with either test alone. However, when two simultaneous tests are used, there is a net gain in sensitivity and a net loss in specificity, compared with either test alone.

Given these results, the decision to use either sequential or simultaneous testing often is based both on the objectives of the testing, including whether testing is being done for screening or diagnostic purposes, and on practical considerations related to the setting in which the testing is being done, including the length of hospital stay, costs, and degree of invasiveness of each of the tests, as well as the extent of third-party insurance coverage.

PREDICTIVE VALUE OF A TEST

So far, we have asked, "How good is the test at identifying people with the disease and people without the disease?" This is an important issue, particularly in screening free-living populations who have no symptoms of the disease being evaluated. In effect, we are asking, "If we screen a population, what proportion of people who have the disease will be correctly identified?" This is clearly an important public health consideration. In the clinical setting, however, a different question may be important for the clinician: "If the test results are positive in this patient, what is the probability that this patient has the disease?" This is called the *positive predictive value* (PPV) of the test. In other words, what proportion of patients who test positive actually have the disease in question? To calculate the PPV, we divide the number of true positives by the total number who tested positive (true positives + false positives).

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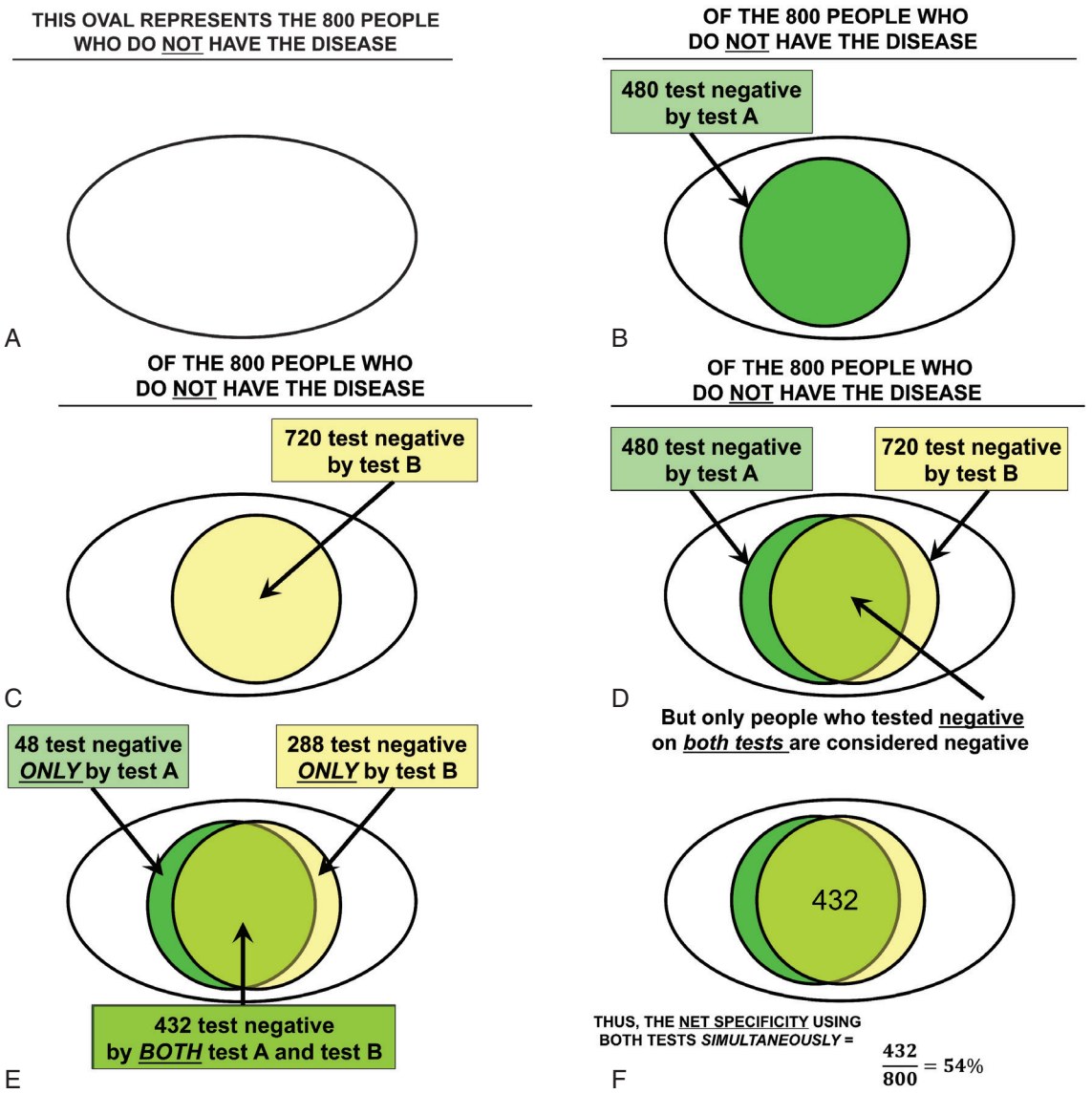

Fig. 5.9 **(A** to **F)** Net specificity: hypothetical example of simultaneous testing. (See explanation in the text under the subheading "Net Specificity Using Two Simultaneous Tests" on page 105.)

Let's return to the example shown in Table 5.1, in which a population of 1,000 persons is screened. As seen in Table 5.7, a 2 × 2 table shows the results of a dichotomous screening test in that population. Of the 1,000 subjects, 180 have a positive test result; of these 180 subjects, 80 have the disease. Therefore the PPV is 80/180, or 44%.

A parallel question can be asked about negative test results: "If the test result is negative, what is the probability that this patient does not have the disease?" This is called the *negative predictive value* (NPV) of the test. It is calculated by dividing the number of true negatives by all those who tested negative (true negatives + false negatives). Looking again at the example in Table 5.7, 820 people have

TABLE 5.6 Results of Screening With Test B

Results of Screening	POPULATION: Disease	POPULATION: No Disease
Positive	180	80
Negative	20	720
Totals	200	800
	Sensitivity = 90%	Specificity = 90%

a negative test result, and of these, 800 do not have the disease. Thus the NPV is 800/820, or 98%.

Every test that a clinician performs—history, physical examination, laboratory tests, x-rays, electrocardiograms, and other procedures—is used to enhance the likelihood of making the correct diagnosis. What they want to know after administering a test to a patient is: "Given this positive test result, what is the likelihood that the patient has the disease?"

Unlike the sensitivity and specificity of the test, which can be considered characteristic of the test being used, the PPV is affected by two factors: the *prevalence* of the disease in the population tested and, when the disease is infrequent, the *specificity* of the test being used. Both of these relationships are discussed in the following sections.

Relationship Between Positive Predictive Value and Disease Prevalence

In the discussion of predictive value that follows, the term *predictive value* is used to denote the *positive* predictive value of the test.

The relationship between predictive value and *disease prevalence* can be seen in the example given in Table 5.8. First, let's direct our attention to the upper part of the table. Assume that we are using a test with a sensitivity of 99% and a specificity of 95% in a population of 10,000 people in which the disease prevalence is 1%. Because the prevalence is 1%, 100 of the 10,000 persons have the disease and 9,900 do not. With a sensitivity of 99%, the test correctly identifies 99 of the 100 people who have the disease. With a specificity of 95%, the test correctly identifies as negative 9,405 of the 9,900 people who do not have the disease. Thus, in this population with a 1% prevalence, 594 people are identified as positive by the test (99 + 495). However, of these 594 people, 495 (83%) are false positives and the PPV is therefore 99/594, or only 17%.

Let's now apply the same test—with the same sensitivity and specificity—to a population with a higher

TABLE 5.7 Predictive Value of a Test

Results of Screening	POPULATION: Disease	POPULATION: No Disease	Totals	
Positive	80	100	180	Positive predictive value = $\frac{80}{180}$ = 44%
Negative	20	800	820	Negative predictive value = $\frac{800}{820}$ = 98%
Totals	100	900	1,000	

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TABLE 5.8 Relationship of Disease Prevalence to Positive Predictive Value

EXAMPLE: SENSITIVITY = 99%, SPECIFICITY = 95%

Disease Prevalence	Test Results	Sick	Not Sick	Totals	Positive Predictive Value
1%	+	99	495	594	$\frac{99}{594} = 17\%$
	−	1	9,405	9,406	
	Totals	100	9,900	10,000	
5%	+	495	475	970	$\frac{495}{970} = 51\%$
	−	5	9,025	9,030	
	Totals	500	9,500	10,000	

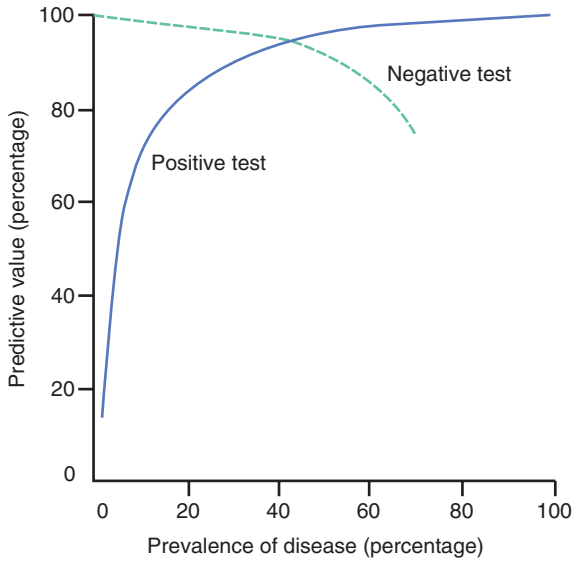

Fig. 5.10 Relationship between disease prevalence and predictive value in a test with 95% sensitivity and 95% specificity. (From Mausner JS, Kramer S. *Mausner and Bahn Epidemiology: An Introductory Text.* Philadelphia: WB Saunders; 1985:221.)

disease prevalence, 5%, as seen in the lower part of Table 5.8. Using calculations similar to those used in the upper part of the table, the PPV is now 51%. Thus the higher prevalence in the screened population has led to a marked increase in the PPV using the same test. Fig. 5.10 shows the relationship between disease prevalence and predictive value from a classic example. Clearly most of the gain in predictive value occurs with increases in prevalence at the lowest rates of disease prevalence.

Why should we be concerned about the relationship between predictive value and disease prevalence? As we have seen, the higher the prevalence, the higher the predictive value. Therefore, a screening program is most productive and more cost-effective if it is directed to a high-risk target population. Screening a total population for a relatively infrequent disease can be a wasteful use of resources and may yield few previously undetected cases relative to the amount of effort involved. However, if a high-risk subset can be identified and screening can be directed to this group, the program is likely to be far more productive. In addition, a high-risk population may be more motivated to participate in such a screening program and more likely to take recommended action if their screening results are positive.

The relationship between predictive value and disease prevalence also shows that the results of any test must be interpreted in the context of the prevalence of the disease in the population from which the subject originates. An interesting example is seen with the measurement of the maternal serum α-fetoprotein (MSAFP) level for prenatal diagnosis of spina bifida. Fig. 5.11 shows the distribution of MSAFP levels in normal unaffected pregnancies and in pregnancies in which the fetus has Down syndrome; spina bifida, which is a neural tube defect; or anencephaly. For the purpose of this example, we will focus on the curves for unaffected pregnancies and spina bifida. Although the distribution of these two curves is bimodal, there is a range in which the curves overlap, and within that range, it may not always be clear to which curve the mother and fetus belong. If MSAFP is in the higher range for an unaffected pregnancy, the true prevalence of spina bifida will be low for the same range. Thus such overlap in the MSAFP in the unaffected pregnancies and those with fetuses with spina bifida has led to the test having a very low PPV, of only 2% to 6%.[2]

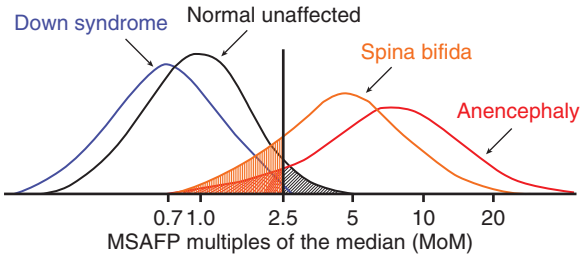

Fig. 5.11 Maternal serum alpha-fetoprotein *(MSAPF)* distribution for singleton pregnancies at 15 to 20 weeks. The screen cutoff value of 2.5 multiples of the median is expected to result in a false-positive rate of up to 5% *(black hatched area)* and false-negative rates of up to 20% for spina bifida *(orange hatched area)* and 10% for anencephaly *(red hatched area)*. (Modified from Prenatal diagnosis. In: Cunningham F, Leveno KJ, Bloom SL, et al., eds. *Williams Obstetrics*. 24th ed. New York: McGraw-Hill; 2013. http://accessmedicine.mhmedical.com.ezp.welch.jhmi.edu/content.aspx?bookid=1057&sectionid=59789152[12]. Accessed June 19, 2017.)

It is possible that the same test can have a very different predictive value when it is administered to a high-risk (high prevalence) population or to a low-risk (low prevalence) population. This has clear clinical implications: A woman may make a decision to terminate a pregnancy, and a physician may formulate advice to such a woman on the basis of the test results. However, the same test result may be interpreted differently, depending on whether the woman comes from a pool of high-risk or low-risk women, which will be reflected in the PPV of the test. Consequently, by itself, the test result may not be sufficient to serve as a guide without taking into account the other considerations just described.

The following true examples highlight the importance of this issue:

> *The head of a firefighters' union consulted a university cardiologist because the fire department physician had read an article in a leading medical journal reporting that a certain electrocardiographic finding was highly predictive of serious, generally unrecognized, coronary heart disease. On the basis of this article, the fire department physician was disqualifying many young, able-bodied firefighters from active duty. The cardiologist read the paper and found that the study had been carried out in hospitalized patients.*

What was the problem? Because hospitalized patients have a much higher prevalence of heart disease than does a group of young, able-bodied firefighters, the fire department physician had erroneously taken the high predictive value obtained in studying a high-prevalence population and inappropriately applied it to a low-prevalence population of healthy firefighters, in whom the same test would actually have a much lower predictive value.

Here is another example:

> *A physician visited his general internist for a regular annual medical examination, which included a stool examination for occult blood. One of the three stool specimens examined in the test was positive. The internist told his physician-patient that the result was of no significance because he regularly encountered many false-positive test results in his busy practice. The test was repeated on three new stool specimens, and all three of the new specimens were now negative. Nevertheless, sensing his patient's lingering concerns, the internist referred his physician-patient to a gastroenterologist. The gastroenterologist said, "In my experience, the positive stool finding is serious. Such a finding is almost always associated with pathologic gastrointestinal disorders. The subsequent negative test results mean nothing, because you could have a tumor that only bleeds intermittently."*

Who was correct in this episode? The answer is that both the general internist and the gastroenterologist were correct. The internist gave his assessment of predictive value based on his experience in his general medical practice—a population with a low prevalence of serious gastrointestinal disease. On the other hand, the gastroenterologist gave his assessment of the predictive value of the test based on his experience in his referral practice—a practice in which most patients are referred because of a likelihood of serious gastrointestinal illness, a high-prevalence population.

Relationship Between Positive Predictive Value and Specificity of the Test

In the discussion that follows, the term *predictive value* is used to denote the PPV of the test.

A second factor that affects the predictive value of a test is the *specificity* of the test. Examples of this are shown first in graphical form and then in tabular form. Fig. 5.12A to D diagrams the results of screening a population; however, the 2 × 2 tables in these figures

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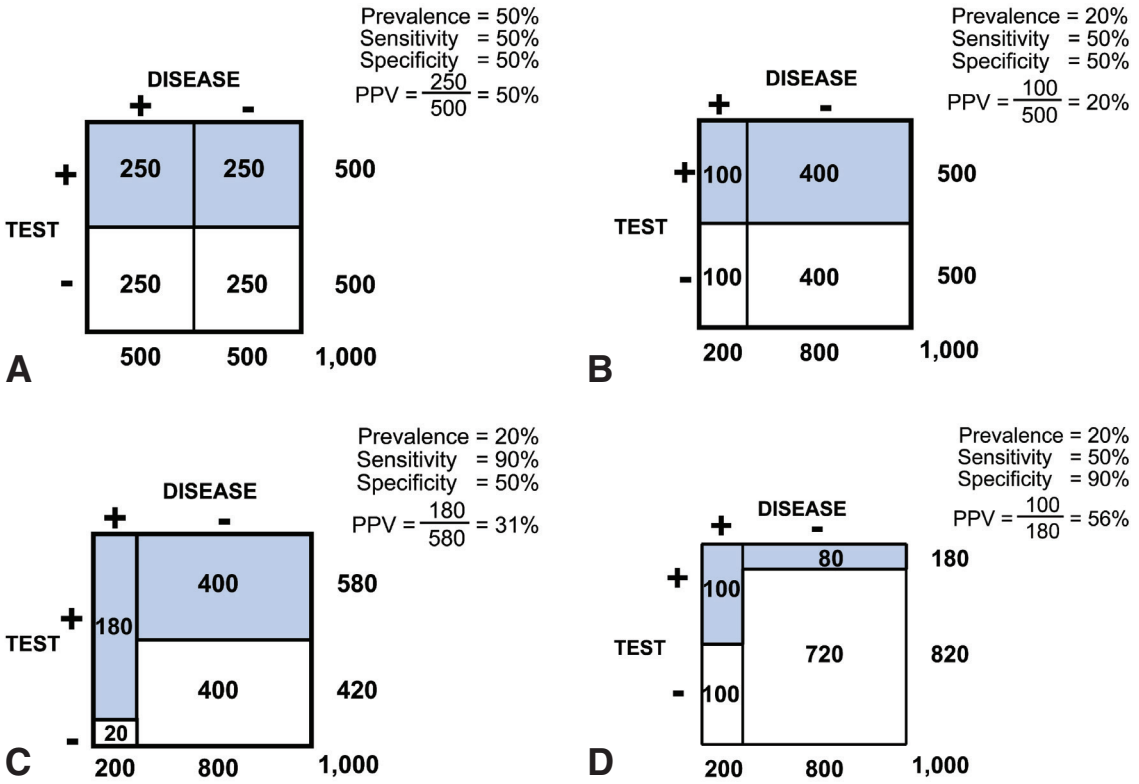

Fig. 5.12 **(A** to **D)** Relationship of specificity to positive predictive value *(PPV)*. (See explanation in the text under the subheading "Relationship Between Positive Predictive Value and Specificity of the Test" on page 111.)

differ from those shown in earlier figures. Each cell is drawn with its size proportional to the population it represents. In each figure the cells that represent persons who tested positive are shaded blue; these are the cells that will be used in calculating the PPV.

Fig. 5.12A presents the baseline screened population that is used in our discussion: a population of 1,000 people in whom the prevalence is 50%; thus 500 people have the disease and 500 do not. In analyzing this figure, we also assume that the screening test that was used has a sensitivity of 50% and a specificity of 50%. Because 500 people tested positive, and 250 of these have the disease, the predictive value is 250/500, or 50%.

Fortunately, the prevalence of most diseases is much lower than 50%; we are generally dealing with relatively infrequent diseases. Therefore Fig. 5.12B assumes a lower prevalence of 20% (although even this would be an unusually high prevalence for most diseases). Both the sensitivity and the specificity remain at 50%. Now only 200 of the 1,000 people have the disease, and the vertical line separating diseased from nondiseased persons is shifted to the left. The predictive value is now calculated as 100/500, or 20%.

Given that we are screening a population with the lower prevalence rate, can we improve the predictive value? What would be the effect on predictive value if we increased the sensitivity of the test? Fig. 5.12C shows the results when we leave the prevalence at 20% and the specificity at 50% but increase the sensitivity to 90%. The predictive value is now 180/580, or 31%—a modest increase.

What if, instead of increasing the sensitivity of the test, we increase its specificity? Fig. 5.12D shows the results when prevalence remains 20% and sensitivity remains 50%, but specificity is increased to 90%. The predictive value is now 100/180, or 56%. Thus, an increase in specificity resulted in a much greater increase in predictive value than the same increase in sensitivity.

TABLE 5.9 Relationship of Specificity to Positive Predictive Value

EXAMPLE: PREVALENCE = 10%, SENSITIVITY = 100%

Specificity	Test Results	Sick	Not Sick	Totals	Predictive Value
70%	+	1,000	2,700	3,700	$\frac{1{,}000}{3{,}700} = 27\%$
	−	0	6,300	6,300	
	Totals	1,000	9,000	10,000	
95%	+	1,000	450	1,450	$\frac{1{,}000}{1{,}450} = 69\%$
	−	0	8,550	8,550	
	Totals	1,000	9,000	10,000	

Why does specificity have a greater effect than sensitivity on predictive value? The answer becomes clear by examining these figures. Because we are dealing with infrequent diseases, most of the population falls to the right of the vertical line. Consequently, any change to the right of the vertical line affects a greater number of people than would a comparable change to the left of the line. Thus, a change in specificity has a greater effect on predictive value than a comparable change in sensitivity. If we were dealing with a high-prevalence disease, the situation may be different.

The effect of changes in specificity on predictive value is also seen in Table 5.9 in a form similar to that used in Table 5.8. As seen in this example, even with 100% sensitivity, a change in specificity from 70% to 95% has a dramatic effect on the PPV.

RELIABILITY (REPEATABILITY) OF TESTS

Let's consider another aspect of assessing diagnostic and screening tests—the question of whether a test is reliable or repeatable. Can the results obtained be replicated (getting the same result) if the test is repeated? Clearly, regardless of the sensitivity and specificity of a test, if the test results cannot be reproduced, the value and usefulness of the test are minimal. However, it is important to emphasize, if the validity of the test is low, reliability may be meaningless. The rest of this chapter focuses on the reliability or repeatability of diagnostic and screening tests. The factors that contribute to the variation between test results are discussed first: intrasubject variation (variation within individual subjects), intraobserver variation (variation in the reading of test results by the same reader), and interobserver variation (variation between those reading the test results).

Intrasubject Variation

The values obtained in measuring many human characteristics often vary over time, even during a short period of 24 hours, or a longer period, such as seasonal variation. Fig. 5.13 shows changes in blood pressure readings over a 24-hour period in 28 normotensive individuals. Variability over time is considerable. This, as well as the conditions under which certain tests are conducted (e.g., shortly after eating or post-exercise, at home or in a physician's office), clearly can lead to different results in the same individual. Therefore, in evaluating any test result, it is important to consider the conditions under which the test was performed, including the time of day.

Intraobserver Variation

Sometimes variation occurs between two or more readings of the same test results made by the same observer. For example, a radiologist who reads the same group of x-rays at two different times may read one or more of the x-rays differently the second time. Tests and examinations differ in the degree to which subjective factors enter into the observer's conclusions, and the greater the subjective element in the reading, the greater the intraobserver variation in readings is likely to be.

Interobserver Variation

Another important consideration is variation between observers. Two examiners often do not give the same result. The extent to which observers agree or disagree is an important issue, whether we are considering physical examinations, laboratory tests, or other means of assessing human characteristics. We therefore need to be able to express the extent of agreement in quantitative terms.

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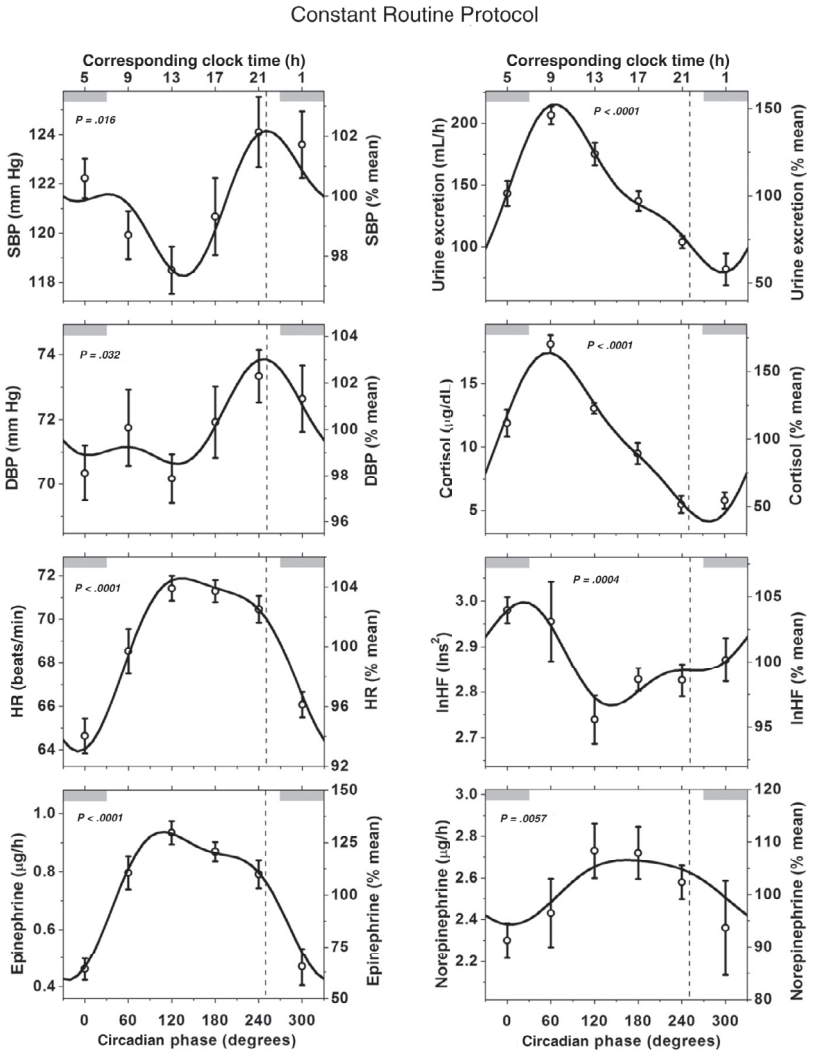

Fig. 5.13 Endogenous circadian variation in blood pressure during the constant routine protocol. *DBP,* Diastolic blood pressure; *HR,* heart rate; *SBP,* systolic blood pressure. (From Shea SA, Hilton MF, Hu K, et al. Existence of an endogenous circadian blood pressure rhythm in humans that peaks in the evening. *Circ Res.* 2011;108:980–984.)

Percent Agreement

Table 5.10 shows a schema for examining variation between observers. Two observers were instructed to categorize each test result into one of the following four categories: abnormal, suspect, doubtful, and normal. This diagram might refer, for example, to readings performed by two radiologists. In this diagram, the readings of observer 1 are cross-tabulated against those of observer 2. The number of readings in each cell is denoted by a letter of the alphabet. Thus A x-rays were read as abnormal by both radiologists. C x-rays were read as abnormal by radiologist 2 and as doubtful by radiologist 1. M x-rays were read as abnormal by radiologist 1 and as normal by radiologist 2.

As seen in Table 5.10, to calculate the overall percent agreement, we add the numbers in all of the cells in which readings by both radiologists agreed (A + F + K + P), divide that sum by the total number of x-rays read, and

TABLE 5.10 Observer or Instrument Variation: Percent Agreement

	Reading No. 1			
Reading No. 2	Abnormal	Suspect	Doubtful	Normal
Abnormal	[A]	B	C	D
Suspect	E	[F]	G	H
Doubtful	I	J	[K]	L
Normal	M	N	O	[P]

$$\text{Percent agreement} = \frac{A + F + K + P}{\text{Total readings}} \times 100$$

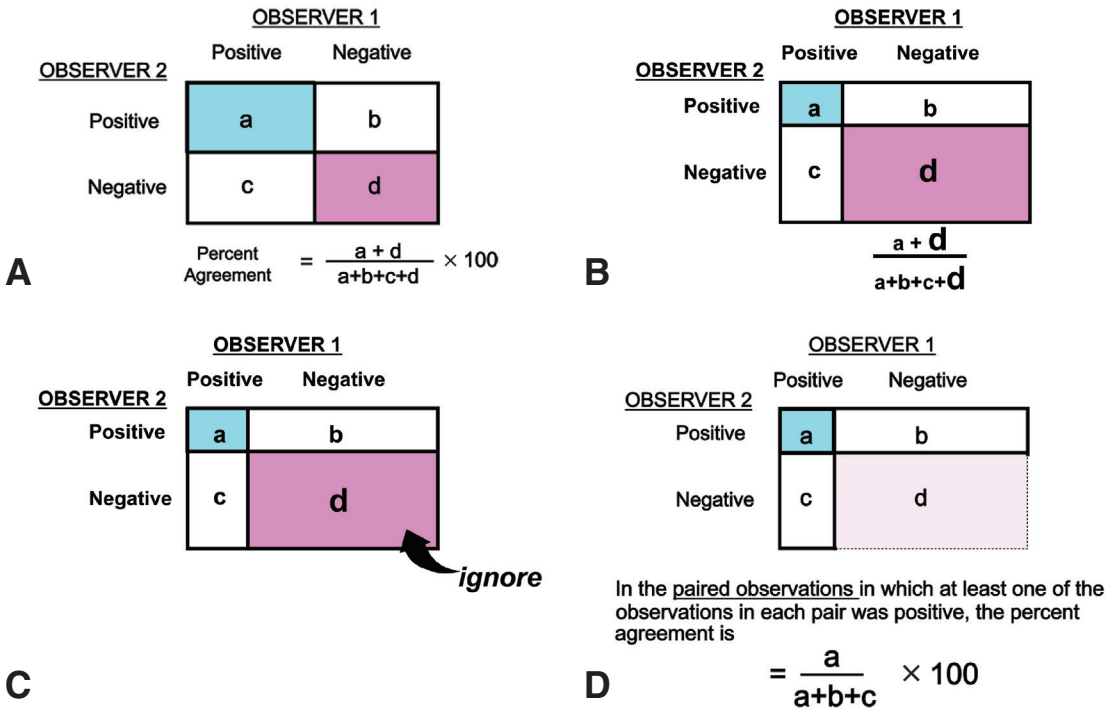

Fig. 5.14 Calculating the percent agreement between two observers. **(A)** Percent agreement when examining paired observations between observer 1 and observer 2. **(B)** Percent agreement when examining paired observations between observer 1 and observer 2, considering that cell d (agreement on the negatives) is very high. **(C)** Percent agreement when examining paired observations between observer 1 and observer 2, ignoring cell d. **(D)** Percent agreement when examining paired observations between observer 1 and observer 2, using only cells a, b, and c for the calculation.

multiply the result by 100 to yield a percentage. Fig. 5.14A shows the use of this approach for a test with possible readings of either "positive" or "negative."

In general, most persons who are tested have negative results. This is shown in Fig. 5.14B, in which the size of each cell is drawn in proportion to the number of people in that cell. There is likely to be considerable agreement between the two observers about these negative, or normal, subjects (cell d). Therefore, when percent agreement is calculated for all study subjects, its value may be high only because of the large number of clearly negative findings (cell d) on which the observers agree. Thus,

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the high value may conceal significant disagreement between the observers in identifying subjects who are considered positive by at least one observer. (A similar phenomenon may happen when most of the values are positive, such as in the case of an outbreak. In this instance, the high percent agreement may conceal the disagreement of observers for the negative results.)

One approach to the problem of a majority of individuals testing negative by both observers, seen in Fig. 5.14C, is to disregard the subjects who were labeled negative by both observers (cell d) and to calculate percent agreement using as a denominator only the subjects who were labeled abnormal by at least one observer (cells a, b, and c; Fig. 5.14D).

Thus, in the paired observations in which at least one of the findings in each pair was positive, the following equation is applicable:

$$\text{Percent agreement} = \frac{a}{a+b+c} \times 100$$

Kappa Statistic

Percent agreement between two observers is often of value in assessing the quality of their observations. The extent to which two observers, such as two physicians or two nurses, for example, agree with one another is often an important index of the quality of the health care being provided. However, the percent agreement between two observers does not entirely depend on the quality of their training and practice. The extent of their agreement is also significantly influenced by the fact that even if two observers use completely different criteria to identify subjects as positive or negative, we would expect the observers to agree about the observations made, at least in some of the participants, solely as a function of chance. What we really want to know is how much better their level of agreement is than that which results just from chance. The answer to this question will presumably tell us, for example, to what extent the education and training that the observers received improved the quality of their readings so that the percent agreement between them was increased beyond what we would expect from chance alone.

This can be shown intuitively in the following example: you are the director of a radiology department that is understaffed one day, and a large number of chest x-rays remain to be read. To solve your problem, you go out to the street and ask a few neighborhood residents, who have no background in biology or medicine, to read the unread x-rays and assess them as either positive or negative. The first person goes through the pile of x-rays, reading them haphazardly as positive, negative, negative, positive, and so on. The second person does the same, in the same way, but completely independent of the first reader. Given that both readers have no knowledge, criteria, or standards for reading x-rays, would any of their readings on a specific x-ray agree? The answer is clearly yes; they would agree in some cases, purely by chance alone.

However, if we want to know how well two observers read x-rays, we might ask, "To what extent do their readings agree *beyond what we would expect by chance alone*?" In other words, to what extent does the agreement between the two observers exceed the level of agreement that would result just from chance? One approach to answering this question is to calculate the kappa statistic, proposed by Cohen in 1960.[3] In this section, we will first discuss the rationale of the kappa statistic and the questions that the kappa statistic is designed to answer. This will be followed by a detailed calculation of the kappa statistic to serve as an example for intrepid readers. Even if you do not follow through the detailed calculation presented here, it is important to be sure that you understand the rationale of the kappa statistic because it is frequently applied both in clinical medicine and in public health.

Rationale of the kappa statistic. In order to understand kappa, we ask two questions. First, how much better is the agreement between the observers' readings than would be expected by chance alone? This can be calculated as the percent agreement observed minus the percent agreement we would expect by chance alone. This is the numerator of kappa:

(Percent agreement observed)
−(Percent agreement expected by chance alone)

Our second question is, "What is the most that the two observers could have improved their agreement over the agreement that would be expected by chance alone?" Clearly the maximum that they could agree would be 100% (full agreement, where the two observers agree completely). Therefore, the most that we could expect them to be able to improve (the denominator of kappa) would be:

100% − (Percent agreement expected by chance alone)

Kappa expresses the extent to which the observed agreement exceeds that which would be expected by chance alone (i.e., percent agreement observed − percent agreement expected by chance alone [numerator]) relative to the maximum that the observers could hope to improve their agreement (i.e., 100% − percent agreement expected by chance alone [denominator]).

Thus, kappa quantifies the extent to which the observed agreement that the observers achieved exceeds that which would be expected by chance alone, and expresses it as the proportion of the maximum improvement that could occur beyond the agreement expected by chance alone. The kappa statistic can be defined by the equation:

$$\text{Kappa} = \frac{\left(\begin{array}{c}\text{Percent agreement}\\ \text{observed}\end{array}\right) - \left(\begin{array}{c}\text{Percent agreement}\\ \text{expected by chance alone}\end{array}\right)}{100\% - \left(\begin{array}{c}\text{Percent agreement}\\ \text{expected by chance alone}\end{array}\right)}$$

Calculation of the kappa statistic: an example. To calculate the numerator for kappa, we must first calculate the amount of agreement that might be expected on the basis of chance alone. As an example, let's consider data on breast density reported on the radiologic classification of breast density on synthetic 2D images as compared with digital 2D mammograms.[4] Fig. 5.15A shows data comparing the findings of the two methods in classifying 309 such cases.

The first question is, "What is the observed agreement between the two types of mammograms?" Fig. 5.15B shows the classifications using the synthetic 2D mammography along the bottom of the table and those of digital 2D mammography along the right margin. Thus synthetic 2D mammography identified 179 (or 58%) of all of the 309 breast images as nondense and 130 (or 42%) of the images as dense. Digital 2D mammography identified 182 (or 59%) of all of the images as nondense and 127 (or 41%) of the images as dense. As discussed earlier, the percent agreement is calculated by the following equation:

$$\text{Percent agreement observed} = \frac{168+116}{309} = 91.9\%$$

That is, the two mammography devices had the same breast image classification on 91.9% of the readings.

The next question is, "If the two types of mammography had used entirely different sets of criteria for classifying a breast image as dense versus nondense, how much agreement would have been expected *solely on the basis of chance*?" Synthetic 2D mammography read 58% of all 309 images (179 images) as being nondense and 42% (130 images) as dense. If these readings had used criteria independent of those used by digital 2D mammography, we would expect that synthetic 2D mammography would read as nondense both 58% of the images that the digital had identified as non dense and 58% of the images that digital 2D mammography had identified as nondense. Therefore, we would expect that 58% (105.56) of the 182 images identified as nondense by digital 2D mammography would be identified as nondense by synthetic 2D mammography, and that 58% (73.44) of the 127 images identified as dense by digital 2D mammography would also be identified as nondense by synthetic 2D mammography (see Fig. 5.14C). Of the 127 images called dense by digital 2D mammography, 42% (53.34) would also be classified as dense by synthetic 2D mammography.

Thus the agreement expected by chance alone would be

$$= \frac{105.56}{309} + \frac{53.34}{309} = \frac{158.9}{309} = 51.4\%$$

of all images read.

Having calculated the figures needed for the numerator and denominator, kappa can now be calculated as follows:

$$\text{Kappa} = \frac{\left(\begin{array}{c}\text{Percent}\\ \text{agreement}\\ \text{observed}\end{array}\right) - \left(\begin{array}{c}\text{Percent agreement}\\ \text{expected by}\\ \text{chance alone}\end{array}\right)}{100 - \left(\begin{array}{c}\text{Percent agreement}\\ \text{expected by}\\ \text{chance alone}\end{array}\right)}$$

$$= \frac{91.9 - 51.4}{100 - 51.4} = \frac{40.5}{48.6} = 83.3\%$$

Landis and Koch[5] suggested that a kappa greater than 0.75 represents excellent agreement beyond chance, a kappa below 0.40 represents poor agreement, and a kappa of 0.40 to 0.75 represents intermediate to good agreement. Testing for the statistical significance

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A

		Synthetic 2D mammography		
		Nondense	Dense	Total by digital 2D mammography
Digital 2D mammography	Nondense	168	14	182 (59%)
	Dense	11	116	127 (41%)
	Total by synthetic 2D mammography	179 (58%)	130 (42%)	309 (100%)

B

		Synthetic 2D mammography		
		Nondense	Dense	Total by digital 2D mammography
Digital 2D mammography	Nondense	168	14	182 (59%)
	Dense	11	116	127 (41%)
	Total by synthetic 2D mammography	179 (58%)	130 (42%)	309 (100%)

Percent agreement observed = $\frac{168 + 116}{309} = 91.9\%$

C

		Synthetic 2D mammography		
		Nondense	Dense	Total by digital 2D mammography
Digital 2D mammography	Nondense	105.56	76.66	182 (59%)
	Dense	73.44	53.34	127 (41%)
	Total by synthetic 2D mammography	179 (58%)	130 (42%)	309 (100%)

Percent agreement expected by chance alone = $\frac{105.56 + 53.34}{309} = 51.4\%$

Fig. 5.15 **(A)** Radiologic classification of breast density on synthetic 2D images as compared with digital 2D mammograms. **(B)** Percent agreement by synthetic and digital 2D mammograms. **(C)** Percent agreement by synthetic and digital 2D mammograms *expected by chance alone*. (From Alshafeiy TI, Wadih A, Nicholson BT, et al. Comparison between digital and synthetic 2D mammograms in breast density interpretation. *AJR Am J Roentgenol.* 2017;209:W36–W41. Reprinted with permission from the American Journal of Roentgenology.)

of kappa is described by Fleiss, who also developed a formula for kappa based on more than two observers.[6]

Considerable discussion has arisen about the appropriate use of kappa, a subject addressed by MacLure and Willett.[7]

Validity of tests with multicategorical results. Validity, as a concept, can be applied to any test against a gold standard. As we explained earlier, we use sensitivity/specificity to validate the results of tests with dichotomous results against a gold standard. What about tests with multicategorical results? In this case, we can calculate the kappa statistic, which we demonstrated earlier as a tool to assess reliability. Thus, what distinguishes validity from reliability is the comparison of the test with a gold standard for the former.

Validity of self-reports. Often, we obtain information on health and disease status by directly asking patients or study participants about their medical history, their habits, and other factors of interest. Most people today know their date of birth, so the assessment of age is usually without significant error. However, many people underreport their weight, their drinking and smoking practices, and other types of risks. Self-reports of sexual behaviors are considered to be subject to considerable error. To overcome these reporting biases, biomarkers have become commonly

used in field studies. For example, Zenilman et al.[8] used a polymerase chain reaction (PCR) assay to detect Y chromosome fragments in self-collected vaginal swabs. This biomarker can detect coitus in women for a 2-week period and can validate self-reports of condom use.[9] More on the problems with self-report will be discussed in Chapter 7 (information bias).

RELATIONSHIP BETWEEN VALIDITY AND RELIABILITY

To conclude this chapter, let's compare validity and reliability using a graphical presentation.

The horizontal line in Fig. 5.16 is a scale of values for a given variable, such as blood glucose level, with the true value indicated. The test results obtained are shown by the curve. The curve is narrow, indicating that the results are quite reliable (repeatable); unfortunately, however, they cluster far from the true value, so they are not valid. Fig. 5.17 shows a curve that is broad and therefore has low reliability. However, the values obtained cluster around the true value and thus are valid. Clearly, what we would like to achieve are results that are both valid and reliable (Fig. 5.18).

It is important to point out that in Fig. 5.18, in which the distribution of the test results is a broad curve centered on the true value, we describe the results as valid. However, the results are valid only for a group (i.e., they tend to cluster around the true value). It is important to remember that what may be valid for a group or a population may not be so for an individual in a clinical setting. When the reliability or repeatability of a test is poor, the validity of the test for a given individual also may be poor. The distinction between group validity and individual validity is therefore important to keep in mind when assessing the quality of diagnostic and screening tests.

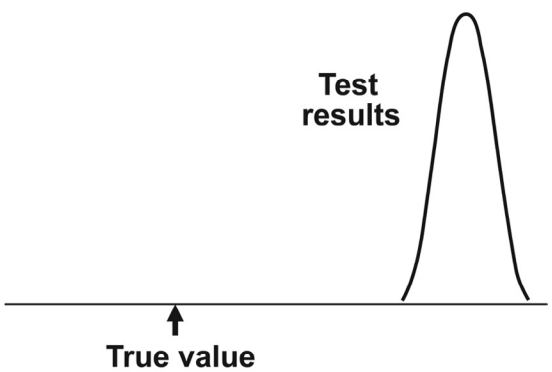

Fig. 5.16 Graph of hypothetical test results that are reliable, but not valid.

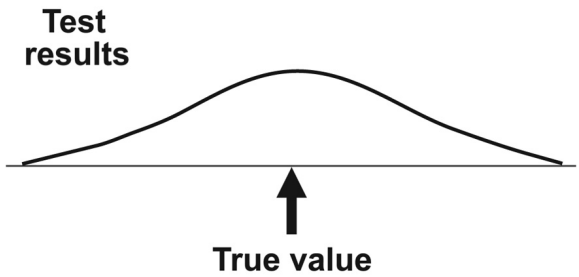

Fig. 5.17 Graph of hypothetical test results that are valid, but not reliable.

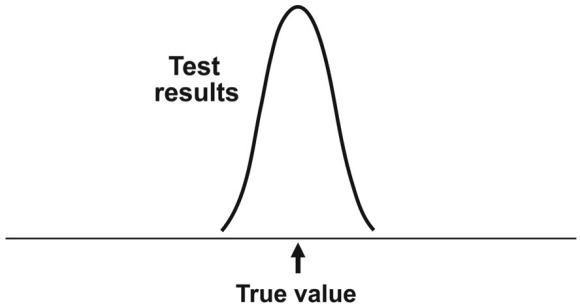

Fig. 5.18 Graph of hypothetical test results that are both valid and reliable.

CONCLUSION

This chapter has discussed the validity of diagnostic and screening tests as measured by their sensitivity and specificity, their predictive value, and the reliability or repeatability of these tests. Clearly, regardless of how sensitive and specific a test may be, if its results cannot be replicated, the test is of little clinical or screening value. All these characteristics must therefore be borne in mind when evaluating such tests, together with the purpose for which the test will be used.

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Review questions on pages 123–124.

APPENDICES TO CHAPTER 5

The text of Chapter 5 focuses on the logic behind the calculation of sensitivity, specificity, and predictive value. Appendix 1 summarizes measures of validity for screening tests to detect the absence or presence of a given disease, the pages in the text where the measures are first introduced, and the interpretation of each measure. For those who prefer to see the formulae for each measure, they are provided in the right-hand column of this table; however, they are not essential for understanding the logic behind the calculation of each measure.

Appendix 1 to Chapter 5 Measures of Test Validity and Their Interpretation

	Measure of Test Validity	Page Numbers	Interpretation	Formula
INDIVIDUAL screening tests	Sensitivity	97	The proportion of those *with* the disease who test *positive*	$\frac{TP}{TP+FN}$
	Specificity	97	The proportion of those *without* the disease who test *negative*	$\frac{TN}{TN+FP}$
	Positive predictive value	107	The proportion of those who test *positive* who do have the disease	$\frac{TP}{TP+FP}$
	Negative predictive value	108	The proportion of those who test *negative* who do NOT have the disease	$\frac{TN}{TN+FN}$
SEQUENTIAL screening tests	Net sensitivity	104	The proportion of those *with* the disease who test *positive* on BOTH Test 1 and Test 2	(Sensitivity of Test 1) × (Sensitivity of Test 2)
	Net specificity	104	The proportion of those *without* the disease who test *negative* on EITHER Test 1 or Test 2	$\left(\begin{array}{c}\text{Specificity of Test 1}\\+\\\text{Specificity of Test 2}\end{array}\right)-\left(\begin{array}{c}\text{Specificity of Test 1}\\\times\\\text{Specificity of Test 2}\end{array}\right)$
SIMULTANEOUS screening tests	Net sensitivity	106	The proportion of those *with* the disease who test *positive* on EITHER Test 1 or Test 2	$\left(\begin{array}{c}\text{Sensitivity of Test 1}\\+\\\text{Sensitivity of Test 2}\end{array}\right)-\left(\begin{array}{c}\text{Sensitivity of Test 1}\\\times\\\text{Sensitivity of Test 2}\end{array}\right)$
	Net specificity	108	The proportion of those *without* the disease who test *negative* on BOTH Test 1 and Test 2	(Specificity of Test 1) × (Specificity of Test 2)

FN, False negatives; *FP*, false positives; *TN*, true negatives; *TP*, true positives.

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Appendix 2 summarizes the three steps required to calculate the kappa statistic.

Appendix 2 to Chapter 5 The Three Steps Required for Calculating Kappa Statistic (κ)

Components	Steps
NUMERATOR How much better is the observed agreement than the agreement expected by chance alone?	STEP 1: $\left(\text{Percent agreement observed}\right) - \left(\text{Percent agreement expected by chance alone}\right)$
DENOMINATOR What is the maximum the observers could have improved upon the agreement expected by chance alone?	STEP 2: $100\% - \left(\text{Percent agreement expected by chance alone}\right)$
$\frac{\text{NUMERATOR}}{\text{DENOMINATOR}} = \text{KAPPA STATISTIC } (\kappa)$ Of the maximum improvement in agreement expected beyond chance alone that could have occurred, what proportion has in fact occurred?	STEP 3: $\kappa = \dfrac{\left(\text{Percent agreement observed}\right) - \left(\text{Percent agreement expected by chance alone}\right)}{100\% - \left(\text{Percent agreement expected by chance alone}\right)}$

A full discussion of kappa and a sample calculation starts on page 116.

REVIEW QUESTIONS FOR CHAPTER 5

Questions 1, 2, and 3 are based on the information given below:

A physical examination was used to screen for breast cancer in 2,500 women with biopsy-proven adenocarcinoma of the breast and in 5,000 age- and race-matched control women. The results of the physical examination were positive (i.e., a mass was palpated) in 1,800 cases and in 800 control women, all of whom showed no evidence of cancer at biopsy.

1. *The sensitivity of the physical examination was: _____*
2. *The specificity of the physical examination was: _____*
3. *The positive predictive value of the physical examination was: _____*

Question 4 is based on the following information:

A screening test is used in the same way in two similar populations, but the proportion of false-positive results among those who test positive in population A is lower than that among those who test positive in population B.

4. *What is the likely explanation for this finding?*
   - **a.** It is impossible to determine what caused the difference
   - **b.** The specificity of the test is lower in population A
   - **c.** The prevalence of disease is lower in population A
   - **d.** The prevalence of disease is higher in population A
   - **e.** The specificity of the test is higher in population A

Question 5 is based on the following information:

A physical examination and an audiometric test were given to 500 persons with suspected hearing problems, of whom 300 were actually found to have them. The results of the examinations were as follows:

	HEARING PROBLEMS	
Result	**Present**	**Absent**
Physical Examination		
Positive	240	40
Negative	60	160
Audiometric Test		
Positive	270	60
Negative	30	140

5. *Compared with the physical examination, the audiometric test is:*
   - **a.** Equally sensitive and specific
   - **b.** Less sensitive and less specific
   - **c.** Less sensitive and more specific
   - **d.** More sensitive and less specific
   - **e.** More sensitive and more specific

Question 6 is based on the following information:

Two pediatricians want to investigate a new laboratory test that identifies streptococcal infections. Dr. Kidd uses the standard culture test, which has a sensitivity of 90% and a specificity of 96%. Dr. Childs uses the new test, which is 96% sensitive and 96% specific.

6. *If 200 patients undergo culture with both tests, which of the following is correct?*
   - **a.** Dr. Kidd will correctly identify more people with streptococcal infection than Dr. Childs
   - **b.** Dr. Kidd will correctly identify fewer people with streptococcal infection than Dr. Childs
   - **c.** Dr. Kidd will correctly identify more people without streptococcal infection than Dr. Childs
   - **d.** The prevalence of streptococcal infection is needed to determine which pediatrician will correctly identify the larger number of people with the disease

Questions 7 and 8 are based on the following information:

A colon cancer screening study is being conducted in Nottingham, England. Individuals 50 to 75 years old will be screened with the Hemoccult test. In this test, a stool sample is tested for the presence of blood.

7. *The Hemoccult test has a sensitivity of 70% and a specificity of 75%. If Nottingham has a prevalence of 12/1,000 for colon cancer, what is the positive predictive value of the test? _____*
8. *If the Hemoccult test result is negative, no further testing is done. If the Hemoccult test result is positive, the individual will have a second stool sample tested with the Hemoccult II test. If this second sample also tests positive for blood, the individual will be referred for more extensive evaluation. What is the effect on net sensitivity and net specificity of this method of screening?*

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a. Net sensitivity and net specificity are both increased
b. Net sensitivity is decreased and net specificity is increased
c. Net sensitivity remains the same and net specificity is increased
d. Net sensitivity is increased and net specificity is decreased
e. The effect on net sensitivity and net specificity cannot be determined from the data

Questions 9 through 12 are based on the information given below:

Two physicians were asked to classify 100 chest x-rays as abnormal or normal independently. The comparison of their classification is shown in the following table:

Classification of Chest X-Rays by Physician 1 Compared With Physician 2

	PHYSICIAN 2		
Physician 1	**Abnormal**	**Normal**	**Total**
Abnormal	40	20	60
Normal	10	30	40
Total	50	50	100

9. *The simple percent agreement between the two physicians out of the total is:* _____
10. *The percent agreement between the two physicians, excluding the x-rays that both physicians classified as normal, is:* _____
11. *The value of kappa is:* _____
12. *This value of kappa represents what level of agreement?*
a. Excellent
b. Intermediate to good
c. Poor

6

The Natural History of Disease: Ways of Expressing Prognosis

LEARNING OBJECTIVES

- To compare five different ways of describing the natural history of disease: case-fatality, 5-year survival, observed survival, median survival time, and relative survival.
- To describe two approaches for calculating observed survival over time: the life table approach and the Kaplan-Meier method.
- To illustrate the use of life tables for examining changes in survival.
- To describe how improvements in available diagnostic methods may affect the estimation of prognosis (stage migration).

At this point, we have learned how diagnostic and screening tests permit the identification of sick and healthy individuals, and also the categorization of stages of disease. Once a person is identified as having a disease, the question arises: *How can we characterize the natural history of the disease in quantitative terms?* Such quantification is important for several reasons. First, it is necessary to describe the *severity* of a disease to establish priorities for public health programs and clinical services. Second, patients often ask questions about *prognosis.* Third, such quantification is important to establish a baseline for natural history, so that as new treatments become available, the effects of these treatments can be compared with the expected outcome without them. This is also important to identify which treatments or management strategies are optimal for different stages of the disease. Furthermore, if different types of therapy are available for a given disease, such as surgical or medical treatments or two different types of surgical procedures, we want to be able to compare the effectiveness of the various types of therapy associated with outcomes. Therefore, to allow such comparisons, we need a quantitative means of expressing the prognosis in groups receiving the different treatments.

This chapter describes some of the ways in which prognosis can be described in quantitative terms for a group of patients. Thus, the natural history of disease (and hence its prognosis) is discussed in this chapter; later chapters discuss the issue of how to intervene in the natural history of disease to improve prognosis: Chapters 10 and 11 discuss how randomized controlled trials are used to select the most appropriate intervention (medical, surgical, or lifestyle), and Chapter 18 discusses how, through screening, disease can be detected at an earlier point than usual in its natural history to maximize the effectiveness of treatment. To discuss prognosis, let's begin with a schematic representation of the natural history of disease in a patient, as shown in Fig. 6.1.

Point A marks the biologic onset of disease. Often, this point cannot be identified because it occurs subclinically, perhaps as a subcellular change, such as an alteration in DNA. At some point in the progression of the disease process (point P), pathologic evidence of disease could be obtained if it were sought by population screening or routinely by a physician conducting a physical examination, probably during a routine screening. This evidence can also be an incidental finding while managing another disease or complaint in the

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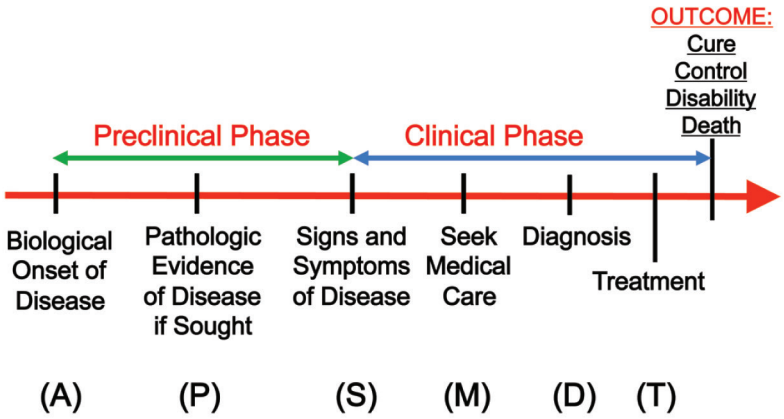

Fig. 6.1 The natural history of disease in a patient.

same patient. Subsequently, signs and symptoms of the disease develop in the patient (point S), and at some time after that, the patient may seek medical care (point M). The patient may then receive a diagnosis (point D), after which treatment may be given (point T). The subsequent course of the disease might result in cure or remission, control of the disease (with or without disability), or even death.

At what point do we begin to quantify survival time? Ideally, we would prefer to do so from the onset of disease. However, this is not generally possible, because the time of biologic onset in an individual is most often not known. If we were to count from the time at which symptoms begin, we would introduce considerable subjective variability in measuring length of survival because we inadvertently ignored the time between the biologic onset of disease to the first symptoms and signs, which could range from hours or days (for an acute infection) to months or years (e.g., as in prostate cancer). In general, to standardize the calculations, duration of survival is counted from the time of diagnosis. However, even with the use of this starting point, variability still occurs, because patients differ in the point at which they seek medical care and physicians differ in their diagnostic or clinical management approaches, even in the presence of clinical practice guidelines. Furthermore, the increasing use of technology and improvement in diagnostic modalities over time introduce additional variability over time—what was true about the natural history of the disease 20 years ago may not be true now. In addition, some diseases, such as certain types of arthritis, are indolent (pain-free) and develop slowly, so that patients may not be able to accurately pinpoint the onset of symptoms or recall the point in time at which they sought medical care. Furthermore, when survival is counted from the time of diagnosis, any patients who may have died before a diagnosis was made are excluded from the count. What effect would this have on our estimates of prognosis?

An important related question is, "How is the diagnosis made?" Is there a clear *pathognomonic* test for the disease in question? Such a test is often not available. Sometimes a disease may be diagnosed by the isolation of an infectious agent, but because people can be carriers of organisms without actually being infected, we do not always know that the isolated organism is the cause of disease. An example of infection without symptoms is given by a large systematic review and meta-analysis which analyzed the global percentage of asymptomatic SARS-CoV-2 infections between February 2020 and February 2021.[1] Using those with confirmed COVID-19 diagnosis, the prevalence of asymptomatic SARS-CoV-2 infections was found to be 41%. This underscores the high risk of community transmission of infection by asymptomatic individuals. For some diseases, we might prefer to make a diagnosis by tissue confirmation taken by biopsy, but there may be variability in the interpretation of tissue slides by different pathologists. An example is the considerable variability of diagnosis of breast ductal carcinoma in situ by three pathologists.[2] An additional issue is that with certain health problems, such as headaches, lower back pain, and dysmenorrhea, a specific tissue diagnosis is not possible. Consequently, when we say that survivorship is measured from the

time of diagnosis, the time frame is not always clear. These issues should be kept in mind as we proceed to discuss different approaches to estimating prognosis.

Prognosis can be expressed either in terms of deaths from the disease or in terms of survivors with the disease. Although both approaches are used in the following discussion, the final end point used for the purposes of our discussion in this example is death. Because death is inevitable, we are not talking about dying versus not dying, but rather about extending the interval time until death occurs following diagnosis. This can also be called *survival time*. Other end points might be used, including the interval from diagnosis to recurrence of disease or from diagnosis to the time of functional impairment, disease-specific complications, disability, or changes in the patient's quality of life, all of which may be affected by the invasiveness of the available treatment, when the treatment was initiated, or the extent to which some of the symptoms can be relieved—even if the patient's life span cannot be extended. These are all important measures, but they are not discussed in this chapter.

CASE-FATALITY

The first way to express prognosis is *case-fatality*, which was first discussed in Chapter 4. Case-fatality is defined as the number of people who die of a disease divided by the number of people who have the disease. Given that a person has the disease, what is the likelihood that they will die of the disease? Note that the denominator for case-fatality is the number of people who have the disease, which makes it a proportion, while sometimes it is incorrectly referred to as a rate. This differs from a *mortality rate*, in which the denominator includes anyone at risk of dying of the disease—which includes both persons who have the disease and persons who do not (yet) have the disease, but in whom it could develop.

Case-fatality does not include any explicit statement of time. However, time is expressed implicitly, because case-fatality is generally used for acute diseases in which death, if it occurs, occurs relatively soon after diagnosis. Thus, if the usual natural history of the disease is known, the term *case-fatality* refers to the period after diagnosis during which death might be expected to occur.

Case-fatality is ideally suited to diseases that are short-term, acute conditions. In chronic diseases, in which death may occur many years after diagnosis and the possibility of death from other causes becomes more likely, case-fatality becomes a less useful measure. For example, in the study of prostate cancer, men with this diagnosis may often die from some other cause, due to the very slow progression of this cancer. We therefore use different approaches for expressing prognosis in such diseases.

PERSON-YEARS

A useful way of expressing mortality is in terms of the number of deaths divided by the person-years over which a group is observed. Because individuals are often observed for different periods of time, the unit used for counting observation time is the person-year. (Person-years were previously discussed in Chapter 3, pages 48.) The number of person-years for two people, each of whom is observed for 5 years, is equal to that of 10 people, each of whom is observed for 1 year—that is, 10 person-years. The numbers of person-years can then be added together and the number of events such as deaths can be calculated per the number of person-years observed.

One problem in using person-years is that each person-year is assumed to be equivalent to every other person-year (i.e., the risk is the same in any person-year observed). However, this may not be true. Consider the situation in Fig. 6.2 showing two examples of 10 person-years: two people each observed for 5 years (top two arrows) and five people each observed for 2 years (bottom five arrows). Are they equivalent?

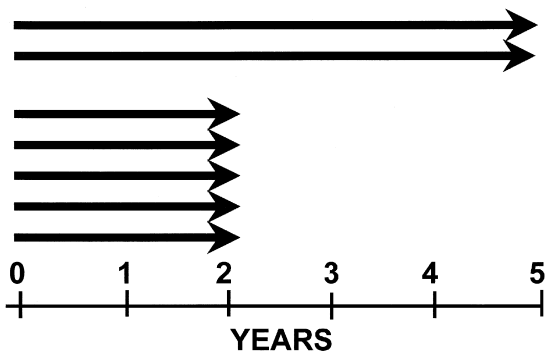

Fig. 6.2 Two examples of 10 person-years: two people, each observed for 5 years, and five people, each observed for 2 years.

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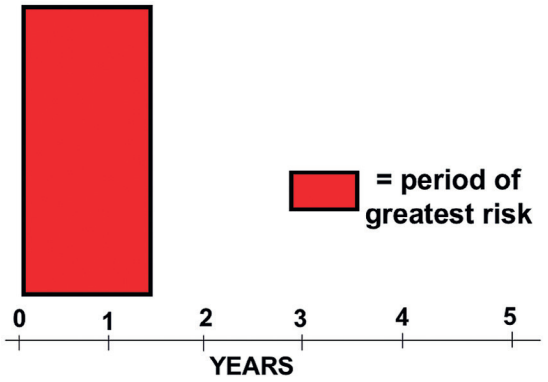

Fig. 6.3 Timing of period of greatest risk is from shortly after diagnosis until about 20 months after diagnosis.

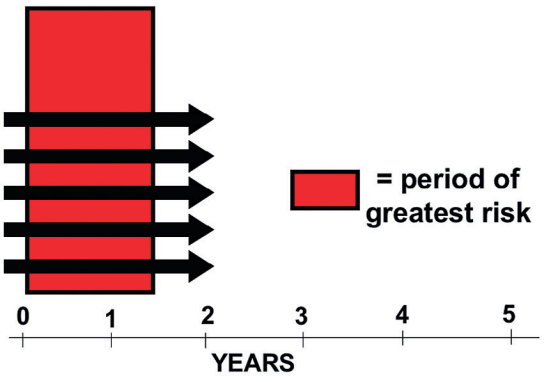

Fig. 6.5 Five people, each observed for 2 years, and the relation to the period of greatest risk.

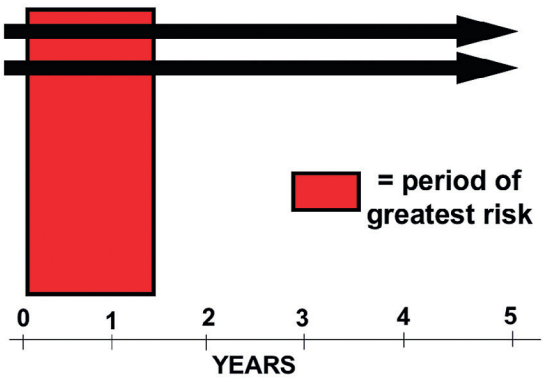

Fig. 6.4 Two people, each observed for 5 years, and the relation to the period of greatest risk.

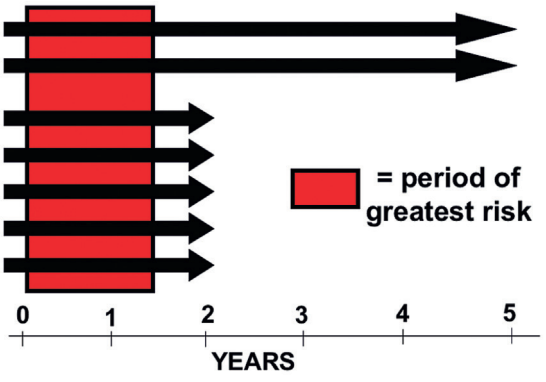

Fig. 6.6 Two examples of 10 person-years in which the period of greatest risk is from shortly after diagnosis until about 20 months after diagnosis.

Suppose the situation is that shown in Fig. 6.3, in which the period of greatest risk of dying is from shortly after diagnosis until about 20 months after diagnosis. Clearly most of the person-years in the first example (i.e., two persons observed for 5 years) will be outside the period of greatest risk (Fig. 6.4), the times from 20 months to 60 months. In contrast, most of the 2-year intervals of the five persons shown in the second example will occur during the period of highest risk (Fig. 6.5). Consequently, when we compare the two examples (Fig. 6.6), more deaths would be expected in the example of five persons observed for 2 years than in the example of two persons observed for 5 years. Despite this issue, person-years are useful as denominators of rates of events in many situations, such as randomized trials (see Chapters 10 and 11) and cohort studies (see Chapter 8). Note that, as discussed in other textbooks,[3] a rate per person-years is equivalent to an average yearly rate. Thus, a rate per person-years can be compared to a Vital Statistics yearly rate based on the period's midpoint population estimate. This is useful when it is of interest to compare rates of per person-years in a study with population rates.

Another way to understand the often unwarranted assumption that person-years is equivalent to persons is to ask whether it is the same to follow 1 smoker for 10 years (10 person-years) and to follow 10 smokers for 1 year, in order to calculate the incidence of lung cancer. Because smoking has a cumulative effect, a smoker followed for 10 years will have a higher risk of developing

lung cancer than the 10 nonsmokers followed for 1 year. Thus, an important assumption when using the person-years approach is that the effect of the risk factor is not cumulative.

It should also be noted that the person-time approach may also be used when considering other time parameters, such as person-months or person-days.

FIVE-YEAR SURVIVAL

Another measure used to express prognosis is *5-year survival.* This term is frequently used in clinical medicine, particularly in evaluating treatments for cancer.

The 5-year survival is the proportion of patients who are alive 5 years after treatment begins or 5 years after diagnosis. (Although 5-year survival is often referred to as a rate, it is actually a proportion.) Despite the widespread use of the 5-year interval, it should be pointed out that there is nothing magical about 5 years. Certainly, no significant biologic change occurs abruptly at 5 years in the natural history of a disease that would justify its use as an end point. However, most deaths from cancer typically occurred during this period after diagnosis when it was first used in the 1950s, so 5-year survival has been used as an index of success in cancer treatment since. Some literature on chronic diseases, such as cardiovascular or kidney diseases, use 10-year survival instead of 5-year survival.

One problem with the use of 5-year survival has become more prominent in recent years with the advent of better screening programs. Let's examine a hypothetical example: Fig. 6.7 shows a timeline for a woman who had biologic onset of breast cancer in 2005. Because the disease was subclinical at that time, she had no symptoms. In 2013, she felt a lump in her breast, which precipitated a visit to her physician, who made the diagnosis. The patient then underwent a mastectomy. In 2015, she died of metastatic cancer. As measured by 5-year survival, which is often used in oncology as a measure of whether therapy has been successful, this patient is not a "success," because she survived for only 2 years after diagnosis.

Let's now imagine that this woman lived in a community in which there was an aggressive breast cancer mammography screening campaign at no cost (lower timeline in Fig. 6.8). As before, biologic onset of disease occurred in 2005, but in 2010, she was identified through screening (mammography and clinical examination of the breast) as having a very small nodule in her breast. She had surgery in 2010 but died in 2015. Because she survived for 5 years after diagnosis and therapy, she would now be identified as a therapeutic "success" in terms of 5-year survival. However, this apparently longer survival is an artifact. Death still occurred in 2015; the patient's life was not lengthened by early detection and therapy. What has happened is that the interval between her diagnosis (and treatment) and her death was increased through earlier diagnosis, but there was no delay in the time of death. (The interval between the earlier diagnosis in 2010, made possible by the screening test, and the later usual time of diagnosis in 2013 is called the *lead time*. This concept is discussed in detail in Chapter 18 in the context of evaluating screening programs.) It is misleading to conclude that, given the

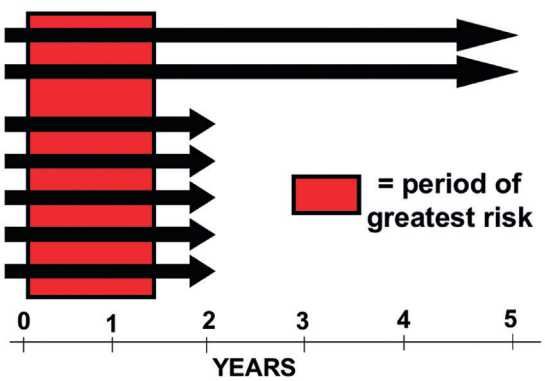

Fig. 6.7 The problem of 5-year survival in a screened population: I. Situation without screening.

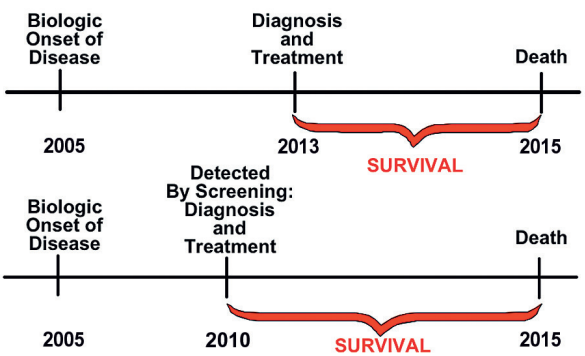

Fig. 6.8 The problem of 5-year survival in a screened population: II. Earlier disease detection by screening.

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patient's 5-year survival, the outcome of the second scenario is any better than that of the first, because no change in the natural history of the disease has occurred, as reflected by the year of death. Indeed, the only change that has taken place is that when the diagnosis was made 3 years earlier (2010 vs. 2013), the patient received medical care for breast cancer, with all its attendant difficulties, for an additional 3 years. Thus, when screening is performed, a higher 5-year survival may be observed, not because people live longer, but only because an earlier diagnosis has been made. This type of potential bias (known as *lead time bias*) must be taken into account in evaluating any screening program before it can be concluded that the screening is beneficial in extending survival.

Another problem with 5-year survival is that if we want to look at the survival experience of a group of patients who were diagnosed less than 5 years ago, we clearly cannot use this criterion, because 5 years of observation are necessary in these patients to calculate 5-year survival. Therefore, if we want to assess a therapy that was introduced less than 5 years ago, 5-year survival is not an appropriate measure.

A final issue relating to 5-year survival is shown in Fig. 6.9. Here we see survival curves for two populations, A and B. Five-year survival is about 10%. However, the curves leading to the same 5-year survival are quite different. Although survival at 5 years is the same in both groups, most of the deaths in group A did not occur until the fifth year, whereas most of the deaths in group B occurred in the first year since they generally had a shorter time to event (death) compared with group A. Thus, despite the identical 5-year survivals, survival during the 5 years is clearly better for those in group A.

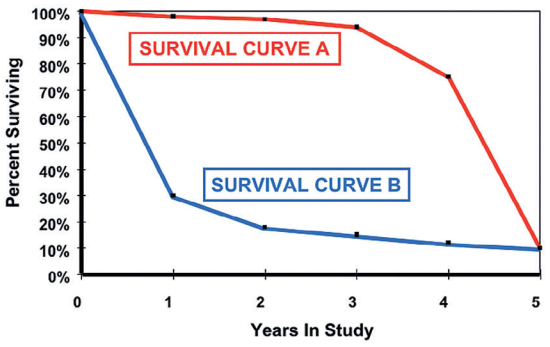

Fig. 6.9 Five-year survival curves in two hypothetical populations.

OBSERVED SURVIVAL

Rationale for the Life Table

Another approach to quantifying prognosis is to use the actual observed survival of patients followed over time, based on knowing the interval within which the event has occurred. For this purpose, we use a *life table*. Life tables have been used by actuaries to estimate risk in populations for centuries when there were no data on individuals. Actuarial methods and models have been applied in a large number of situations, including property/casualty, life insurance, pensions and health insurance, among others. Actuaries are credentialed, with a foundation of statistics and probability, stochastic processes, and actuarial methods and models.

Let's examine the conceptual framework underlying the calculation of survival rates using a life table, especially when the exact event time is not known, but rather we use the interval within which the event took place.

Table 6.1 shows a hypothetical study of treatment results in patients who were treated from 2010 to 2014 and followed to 2015. (By just glancing at this table, you can tell that the example is hypothetical, because the title indicates that no patients were lost to follow-up! However, there may have been administrative censoring in which the researcher removed some participants from further analysis.)

For each calendar year of treatment, the table shows the number of patients enrolled in treatment and the number of patients alive at each calendar year after the initiation of that treatment. For example, of 84 patients enrolled in treatment in 2010, 44 were alive in 2011, a year after beginning treatment; 21 were alive in 2012; and so on.

The results in Table 6.1 include all the data available for assessing the treatment. If we want to describe the prognosis in these treated patients using all of the data in the table, obviously we cannot use 5-year survival, because the entire group of 375 patients has not been observed for 5 years. We could calculate 5-year survival using only the first 84 patients who were enrolled in 2010 and observed until 2015, because they were the only ones observed for 5 years. However, this would require us to discard the rest of the data, which would be unfortunate, given the effort and expense involved in obtaining the data, and also given the additional light that the survival experience of those patients

TABLE 6.1 Hypothetical Study of Treatment Results in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up)

		NUMBER ALIVE ON ANNIVERSARY OF TREATMENT				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62		31	14	10	6
2021	93			50	20	13
2022	60				29	16
2023	76					43

TABLE 6.2 Rearrangement of Data in Table 6.1, Showing Survival Tabulated by Years Since Enrollment in Treatment (None Lost to Follow-Up)

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				

would cast on the effectiveness of the treatment. The question is: How can we use *all* of the information in Table 6.1 to describe the survival experience of the patients in this study?

To use all of the data, we rearrange the data from Table 6.1 as shown in Table 6.2. In this table, the data show the number of patients who started treatment each calendar year and the number of those who remained alive on each anniversary of the initiation of treatment. The patients who started treatment in 2014 were observed for only 1 year, because the study ended in 2015.

With the data in this format, how do we use the table? First we ask, "What is the probability of surviving for 1 year after the beginning of treatment?" To answer this, we divide the total number of patients who were alive 1 year after the initiation of treatment (197) by the total number of patients who started treatment (375; Table 6.3).

The probability of surviving the first year (P_1) is:

$$P_1 = \frac{197}{375} = 0.525$$

Next, we ask, "What is the probability that, having survived the first year after beginning treatment, the patients will survive the second year?" We see in Table 6.4 that 197 people survived the first year, but for 43 of them (the ones who were enrolled in 2014), we have no further information because they were observed for only 1 year. Because 71 survived the second year, we calculate the probability of surviving the second year, if the patient survived the first year (P_2), as:

$$P_2 = \frac{71}{197 - 43} = 0.461$$

In the denominator we subtract the 43 patients for whom we have no data for the second year.

Following this approach, we next ask, "Given that a person has survived to the end of the second year, what is the probability, on average, that he or she will survive to the end of the third year?"

In Table 6.5, we see that 36 survived the third year. Although 71 had survived the second year, we have no further information on survival for 16 of them because they

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TABLE 6.3 Analysis of Survival in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up): I

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				
Totals	375	197				

$$P_1 = \text{Probability of surviving the 1st year} = \frac{197}{375} = 0.525$$

TABLE 6.4 Analysis of Survival in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up): II

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				
Totals		197	71			

$$P_2 = \text{Probability of surviving the 2nd year} = \frac{71}{197 - 43} = 0.461$$

TABLE 6.5 Analysis of Survival in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up): III

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				
Totals			71	36		

$$P_3 = \text{Probability of surviving the 3rd year} = \frac{36}{71 - 16} = 0.655$$

TABLE 6.6 Analysis of Survival in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up): IV

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				
Totals				36	16	

$$P_4 = \text{Probability of surviving the 4th year} = \frac{16}{36 - 13} = 0.696$$

TABLE 6.7 Analysis of Survival in Patients Treated From 2010–2014 and Followed to 2015 (None Lost to Follow-Up): V

		NUMBER ALIVE AT END OF YEAR				
Year of Treatment	No. of Patients Treated	2019	2020	2021	2022	2023
2019	84	44	21	13	10	8
2020	62	31	14	10	6	
2021	93	50	20	13		
2022	60	29	16			
2023	76	43				
Totals					16	8

$$P_5 = \text{Probability of surviving the 5th year} = \frac{8}{16 - 6} = 0.800$$

were enrolled late in the study. Therefore, we subtract 16 from 71 and calculate the probability of surviving the third year, given survival to the end of the second year (P_3), as:

$$P_3 = \frac{36}{71-16} = 0.655$$

We then ask, "If a person survives to the end of the third year, what is the probability that he or she will survive to the end of the fourth year?"

As seen in Table 6.6, a total of 36 people survived the third year, but we have no further information for 13 of them. Because 16 survived the fourth year, the probability of surviving the fourth year, if the person has survived the third year (P_4), is:

$$P_4 = \frac{16}{36-13} = 0.696$$

Finally, we do the same calculation for the fifth year (Table 6.7). We see that 16 people survived the fourth year, but that no further information is available for 6 of them.

Because 8 people were alive at the end of the fifth year, the probability of surviving the fifth year, if the person has survived the fourth year (P_5), is:

$$P_5 = \frac{8}{16-6} = 0.800$$

Using all of the data that we have calculated, we ask, "What is the probability of surviving for all 5 years?" Box 6.1 shows all of the probabilities of surviving for each individual year that we have calculated.

Now we can answer the question, "If a person is enrolled in the study, what is the probability that he or she will survive 5 years after beginning treatment?" The

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BOX 6.1 Probability of Survival for Each Year of the Study

P_1 = Probability of surviving the 1st year $= \frac{197}{375} = 0.525 = 52.5\%$

P_2 = Probability of surviving the 2nd year given survival to the end of the 1st year $= \frac{71}{197-43} = 0.461 = 46.1\%$

P_3 = Probability of surviving the 3rd year given survival to the end of the 2nd year $= \frac{36}{71-16} = 0.655 = 65.5\%$

P_4 = Probability of surviving the 4th year given survival to the end of the 3rd year $= \frac{16}{36-13} = 0.696 = 69.6\%$

P_5 = Probability of surviving the 5th year given survival to the end of the 4th year $= \frac{8}{16-6} = 0.800 = 80.0\%$

BOX 6.2 Cumulative Probabilities of Surviving Different Lengths of Time

Probability of surviving 1 year = $P_1 = 0.525 = 52.5\%$
Probability of surviving 2 years = $P_1 \times P_2 = 0.525 \times 0.461 = 0.242 = 24.2\%$
Probability of surviving 3 years = $P_1 \times P_2 \times P_3 = 0.525 \times 0.461 \times 0.655 = 0.159 = 15.9\%$
Probability of surviving 4 years = $P_1 \times P_2 \times P_3 \times P_4 = 0.525 \times 0.461 \times 0.655 \times 0.696 = 0.110 = 11.0\%$
Probability of surviving 5 years = $P_1 \times P_2 \times P_3 \times P_4 \times P_5 = 0.525 \times 0.461 \times 0.655 \times 0.696 \times 0.800 = 0.088 = 8.8\%$

probability of surviving for 5 years is the product of each of the probabilities of surviving each year, shown in Box 6.1. So the probability of surviving for 5 years is:

$$= P_1 \times P_2 \times P_3 \times P_4 \times P_5$$
$$= 0.525 \times 0.461 \times 0.655 \times 0.696 \times 0.800$$
$$= 0.088, \text{ or } 8.8\%$$

The probabilities for surviving different lengths of time are shown in Box 6.2. These calculations can be presented graphically in a survival curve, as seen in Fig. 6.10. Note that these calculations use all of the data we have obtained, including the data for patients who were not observed for the full 5 years of the study. As a result, the use of data is economical and efficient.

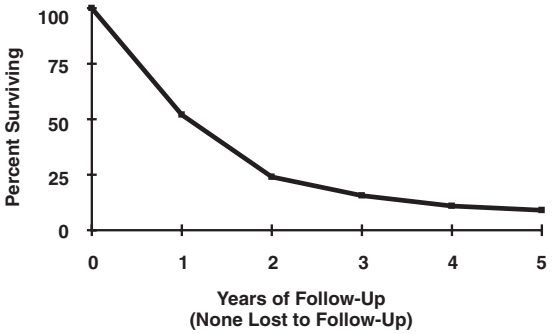

Fig. 6.10 Survival curve for a hypothetical example of patients treated from 2010–2014 and followed until 2015.

Calculating a Life Table

Let's now view the data from this example in the standard tabular form in which they are usually presented for calculating a life table. In the example just discussed, the persons for whom data were not available for the full 5 years of the study were those who were enrolled sometime after the study had started, so they were not observed for the full 5-year period. In virtually every survival study, however, subjects are also lost to follow-up. Either they cannot be found or they decline to continue participating in the study. In calculating the life table, persons for whom data are not available for the full period of follow-up—either because follow-up was not possible or because they were enrolled after the study was started—are called *withdrawals* (or *losses to follow-up* or *administratively censored observations*).

Table 6.8 shows the data from this example with information provided about the number of deaths and the number of withdrawals in each interval. The columns are numbered merely for reference (i.e., there is no meaning inherent to the numbering). The row directly under the column labels gives the terms that are

TABLE 6.8 Rearrangement of Data in Standard Format for Life Table Calculations

(1) Interval Since Beginning Treatment	(2) Alive at Beginning of Interval	(3) Died During Interval	(4) Withdrew During Interval
x	l_x	d_x	w_x
1st year	375	178	0
2nd year	197	83	43
3rd year	71	19	16
4th year	36	7	13
5th year	16	2	6

often used in life table calculations. The next five rows of the table give data for the 5 years of the study.

The columns are as follows:

Column (1): The interval since beginning treatment.

Column (2): The number of study subjects who were alive at the beginning of each interval.

Column (3): The number of study subjects who died during that interval.

Column (4): The number who "withdrew" during the interval—that is, the number of study subjects who could not be followed for the full study period, either because they were lost to follow-up, refused to continue in the study or because they were enrolled after the study had started.

Table 6.9 adds four additional columns to Table 6.8. These columns show the calculations. The new columns are as follows:

Column (5): The number of people who are effectively at risk of dying during the interval. Losses to follow-up (withdrawals) during each time interval are assumed to have occurred uniformly during the entire interval. (This assumption is most likely to hold when the interval is short.) We therefore assume that, on average, they were at risk for *half* the interval. Consequently, to calculate the number of people at risk during each interval, we subtract half the withdrawals during that interval as indicated in the heading for column 5.

Column (6): The proportion who died during the interval is calculated by dividing:

$$\frac{\text{The number who died during the interval (column 3)}}{\text{The number who were effectively at risk of dying during the interval (column 5)}}$$

Column (7): The proportion who did not die during the interval—that is, the proportion of those who were alive at the beginning of the interval and who survived that entire interval = 1.0 − proportion who died during the interval (column 6).

Column (8): The proportion who survived from the point at which they were enrolled in the study to the end of this interval (cumulative survival). This is obtained by multiplying the proportion who were

TABLE 6.9 Calculating a Life Table

(1) Interval Since Beginning Treatment	(2) Alive at Beginning of Interval	(3) Died During Interval	(4) Withdrew During Interval	(5) Effective No. Exposed to Risk of Dying During Interval: Col (2) − $\frac{1}{2}$ [Col (4)]	(6) Proportion Who Died During Interval: $\frac{\text{Col (3)}}{\text{Col (2)}}$	(7) Proportion Who Did Not Die During Interval: 1 − Col (6)	(8) Cumulative Proportion Who Survived From Enrollment to End of Interval: Cumulative Survival
x	l_x	d_x	w_x	l'_x	q_x	p_x	P_x
1st year	375	178	0	375.0	0.475	0.525	0.525
2nd year	197	83	43	175.5	0.473	0.527	0.277
3rd year	71	19	16	63.0	0.302	0.698	0.193
4th year	36	7	13	29.5	0.237	0.763	0.147
5th year	16	2	6	13.0	0.154	0.846	0.124

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alive at the beginning of this interval and who survived this interval by the proportion who had survived from enrollment through the end of the previous interval. Thus, each of the figures in column 8 gives the proportion of people enrolled in the study who survived to the end of each interval. This will be demonstrated by calculating the first two rows of Table 6.9.

Let's look at the data for the first year. (In these calculations, we will round the results at each step and use the rounded figures in the next calculation. In reality, however, when life tables are calculated, the unrounded figures are used for calculating each subsequent interval, and at the end of all the calculations, all the figures are rounded for purposes of presenting the results.) There were 375 subjects enrolled in the study who were alive at the beginning of the first year after enrollment (column 2). Of these, 178 died during the first year (column 3). All subjects were followed for the first year, so there were no withdrawals (column 4). Consequently 375 people were effectively at risk for dying during this interval (column 5). The proportion who died during this interval was 0.475: 178 (the number who died [column 3]) divided by 375 (the number who were at risk for dying [column 5]). The proportion who did not die during the interval is 1.0 − [the proportion who died (1.0 − 0.475)] = 0.525 (column 7). For the first year after enrollment, this is also the proportion who survived from enrollment to the end of the interval (column 8).

Now let's look at the data for the second year. These calculations are important to understand because they serve as the model for calculating each successive year in the life table.

To calculate the number of subjects alive at the start of the second year, we start with the number alive at the beginning of the *first* year and subtract from that number the number of deaths and withdrawals during that year. At the start of the second year, therefore, 197 subjects were alive at the beginning of the interval (column 2 [375 − 178 − 0]). Of these, 83 died during the second year (column 3). There were 43 withdrawals who had been observed for only 1 year (column 4). As discussed earlier, we subtract half of the withdrawals, 21.5 (43/2), from the 197 who were alive at the start of the interval, yielding 175.5 people who were effectively at risk for dying during this interval (column 5). The proportion who died during this interval (column 6) was 0.473—that is, 83 (the number who died [column 3]) divided by 175.5 (the number who were at risk for dying [column 5]). The proportion who did not die during the interval is 1.0 − the proportion who died (1.0 − 0.473) = 0.527 (column 7). The proportion of subjects who survived from the start of treatment to the end of the second year is the product of 0.525 (the proportion who had survived from the start of treatment to the end of the first year—that is, the beginning of the second year) multiplied by 0.527 (the proportion of people who were alive at the beginning of the second year and survived to the end of the second year) = 0.277 (column 8). Thus 27.7% of the subjects survived from the beginning of treatment to the end of the second year. Looking at the last entry in column 8, we see that 12.4% of all individuals enrolled in the study survived to the end of the fifth year.

Work through the remaining years in Table 6.9 to be sure you understand the concepts and calculations involved.

THE KAPLAN-MEIER METHOD

In contrast to the life tables approach just demonstrated, in the Kaplan-Meier method,[4] predetermined intervals (such as 1 month or 1 year) are not used. Rather, we identify the exact point in time when each death, or the event of interest, occurred so that each death, or event, terminates the previous interval and a new interval (and a new row in the Kaplan-Meier table) is started. The number of persons who died at that point is used as the numerator, and the number alive up to that point (including those who died at that time point) is used as the denominator, after any withdrawals that occurred before that point are subtracted.

Let's look at the small hypothetical study shown in Fig. 6.11. Six patients were studied, of whom four died and two were lost to follow-up ("withdrawals"). The deaths occurred at 4, 10, 14, and 24 months after enrollment in the study. The data are set up as shown in Table 6.10:

Column (1): The times for each death from the time of enrollment (time that treatment was initiated, also named "time to event").

Column (2): The number of patients who were alive and followed at the time of that death, including those who died at that time.

Column (3): The number who died at that time.

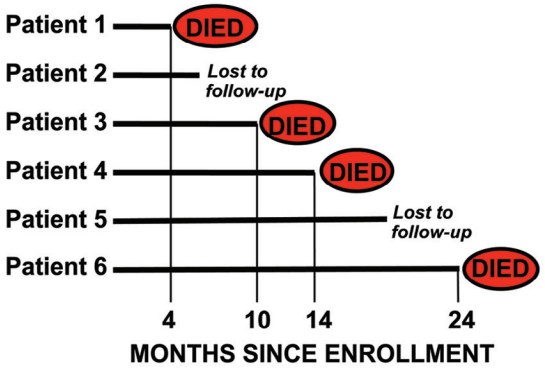

Fig. 6.11 Hypothetical example of a study of six patients analyzed by the Kaplan-Meier method.

Column (4): The proportion of those who were alive and followed (column 2) who died at that time (column 3) (column 3/column 2).

Column (5): The proportion of those who were alive and survived (1.0 − column 4).

Column (6): Cumulative survival (the proportion of those who were initially enrolled and survived to that point).

Let's consider the first row of the table. The first death occurred at 4 months, at which time six patients were alive and followed (see Fig. 6.11). One death occurred at this point (column 3), for a proportion of 1/6 = 0.167 (column 4). The proportion who survived at that time is 1.0 − column 4, or 1.0 − 0.167 = 0.833 (column 5), which is also the cumulative survival at this point (column 6).

The next death occurred 10 months after the initial enrollment of the six patients in the study, and data for this time are seen in the next row of the table. Although only one death had occurred before this one, the number alive and followed is only four because there had also been a withdrawal before this point (not shown in the table but seen in Fig. 6.11). Thus, there was one death (column 3), and as seen in Table 6.10, the proportion who died is 1/4, or 0.250 (column 4). The proportion who survived is 1.0 − column 4, or 1.0 − 0.250 = 0.750 (column 5). Finally, the cumulative proportion surviving (column 6) is the product of the proportion who survived to the end of the previous interval (until just before the previous death) seen in column 6 of the first row (0.833) and the proportion who survived from that time until just before the second death (second row in column 5, 0.750). The product = 0.625—that is, 62.5% of the original enrollees survived to this point. Review the next two rows of the table to be sure that you understand the concepts and calculations involved.

The values calculated in column 6 are plotted as seen in Fig. 6.12. Note that the data are plotted in a stepwise fashion rather than in a smoothed slope because, after the drop in survival resulting from each death, survival then remains unchanged until the next death occurs.

When information on the exact time of death is available, the Kaplan-Meier method clearly makes fullest use of this information because the data are used to define the intervals, instead of predetermined arbitrary intervals used in the life tables method. The use of modern technology to communicate with patients, conducted simultaneously in different study sites, and electronically linking mortality data to research databases allow researchers to identify the time of event. In addition, computer programs are readily available that make the Kaplan-Meier method easily calculated for large

TABLE 6.10 Calculating Survival Using the Kaplan-Meier Method[a]

(1) Times to Deaths From Starting Treatment (Months)	(2) No. Alive at Each Time	(3) No. Who Died at Each Time	(4) Proportion Who Died at That Time: Col (3) / Col (2)	(5) Proportion Who Survived at That Time: 1 − Col (4)	(6) Cumulative Proportion Who Survived to That Time: Cumulative Survival
4	6	1	0.167	0.833	0.833
10	4	1	0.250	0.750	0.625
14	3	1	0.333	0.667	0.417
24	1	1	1.000	0.000	0.000

[a]See text and Fig. 6.11 regarding withdrawals.

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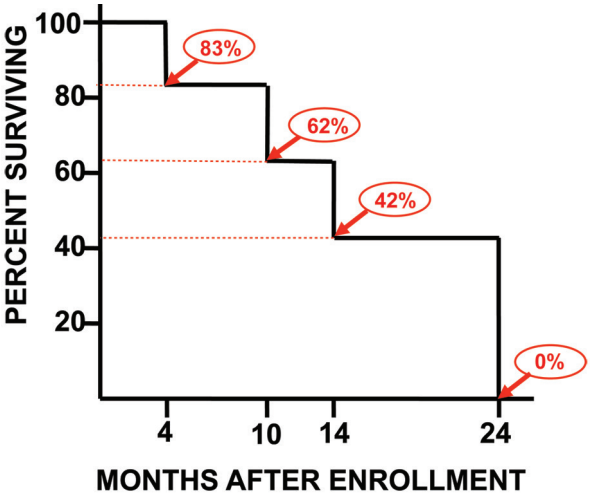


Fig. 6.12 Kaplan-Meier plot of the hypothetical survival study of six patients shown in Fig. 6.11. Percentages in red show cumulative proportions surviving after each of the deaths shown in Fig. 6.11 and are taken from column 6 in Table 6.10. (See discussion of the Kaplan-Meier method on page 136.)

data sets as well. The majority of longitudinal studies in the published literature now report data on survival using the Kaplan-Meier method. For example, in 2000, Rosenhek and colleagues reported a study of patients with asymptomatic, but severe, aortic stenosis.[5] An unresolved issue was whether patients with asymptomatic disease should have their aortic valves replaced. The investigators examined the natural history of this condition to assess the overall survival of these patients and to identify predictors of outcome. Chertow and colleagues[6] studied the association between the use of vadadustat, an investigational hypoxia-inducible factor prolyl hydroxylase inhibitor for anemia management, vs. darbepoetin alfa (an injectable standard of care) and major adverse cardiovascular events (MACE) in a randomized, open-label clinical trial of 3476 patients with anemia and chronic kidney disease not undergoing dialysis.[7] Over a median duration of follow-up of approximately 1.7 years, the *hazard ratio* (a type of relative risk that takes into consideration time to event) for MACE comparing vadadustat to darbepoetin alfa was 1.17 (95% confidence interval, 1.01–1.36). Fig. 6.13 shows their Kaplan-Meier analysis of MACE events over the trial duration. The separation of the two curves starting

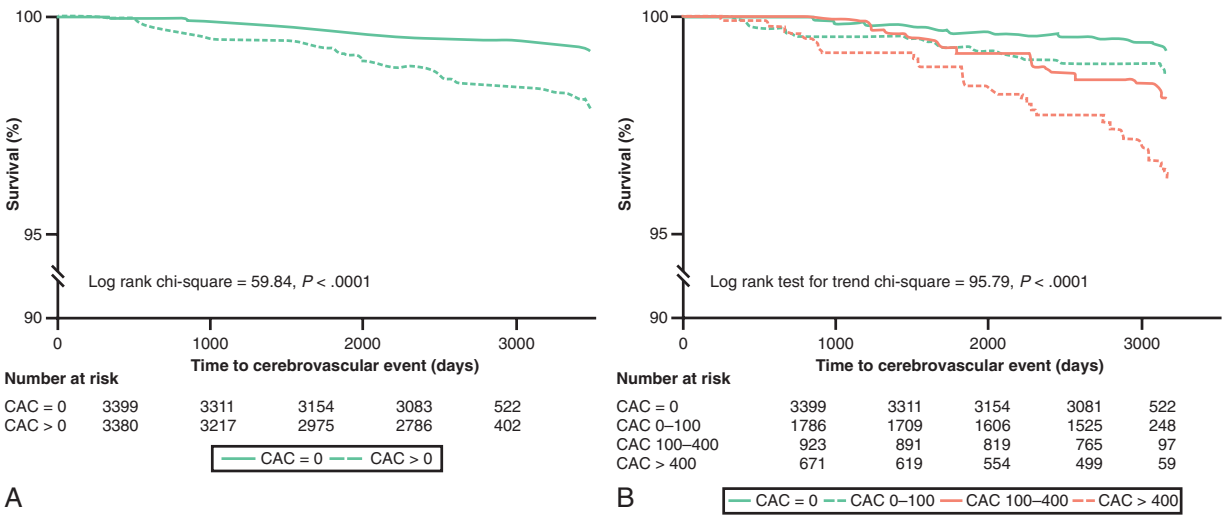
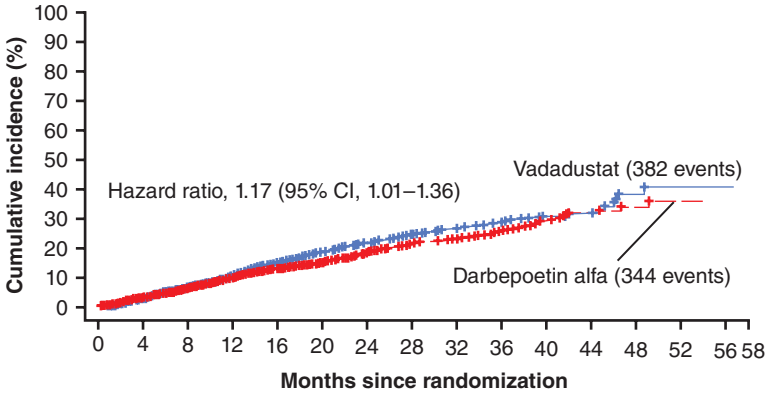


Fig. 6.13 **(A)** Kaplan-Meier analysis showing the event-free survival of participants with and without coronary artery calcium *(CAC)* and incident cerebrovascular events (CVE) in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort. **(B)** Kaplan-Meier analysis showing the CVE event-free survival of participants with 0, 0 to 100, >100 to 400, and >400 CAC (Agatston units) and incident CVE in the MESA cohort. (From Gibson AO, Blaha MJ, Arnan MK, et al. Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. *JACC Cardiovasc Imaging*. 2014;7:1108–1115.)



No. at Risk															
Vadadustat	1739	1668	1587	1301	1108	931	759	588	459	311	185	97	30	4	1	0
Darbepoetin alfa	1732	1674	1618	1329	1129	961	774	621	505	346	213	103	43	6	0	

Fig. 6.14 Major adverse cardiovascular event (MACE). (From Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med.* 2021;384(17):1589–1600.)

around 16 months post randomization indicates risk of exposure to the investigational drug compared to the standard of care (Fig 6.14).

ASSUMPTIONS MADE IN USING LIFE TABLES AND KAPLAN-MEIER METHOD

Two important assumptions are made in using both life tables and Kaplan-Meier methods. The first is that there has been no secular (temporal) change in the effectiveness of treatment or in survivorship over calendar time. That is, we assume that over the period of the study, there has been no improvement in treatment and that survivorship in one calendar year of the study is the same as in another calendar year of the study. Clearly, if a study is conducted over many years, this assumption may not be valid because, fortunately, therapies improve over time. If we are concerned that the effectiveness of therapy may have changed over the course of the study, we could examine the early data separately from the later data. If they seem to differ, the early and later periods could be analyzed separately and the effects compared.

The second assumption relates to follow-up of persons enrolled in the study. In virtually every real-life study, participants are lost to follow-up. People can be lost to follow-up for many reasons. Some may die and may not be traced. Some may die of causes unrelated to the study hypothesis (for example, death from breast cancer when the main outcome is stroke). Some may move or seek care elsewhere. Some may be lost because their disease disappears and they feel well. In most studies, we do not know the actual reasons for losses to follow-up. How can we deal with the problem of people lost to follow-up for whom we therefore have no further information on survival? Since we have baseline data on these people, we could compare the characteristics of the persons lost to follow-up with those of persons who remained in the study. If a large proportion of the study population is lost to follow-up, the findings of the study will be less valid and hence reduce the generalizability of our findings. The challenge is to minimize losses to follow-up. In any case, the second assumption made in survival analysis is that the survival experience of people who are lost to follow-up is the same as the experience of those who are followed up (also named, "not-informative censoring"). Although this assumption is made for purposes of calculation, in actual fact its validity may often be questionable. For mortality, however, the assumption can be verified by means of linkage with the United States National Death Index, which allows comparing the mortality of those lost to follow up with those who continue to be followed up.

Although the term *survival analysis* or *life tables* might suggest that these methods are useful only for calculating survival, this is not so. Death need not be the end point in

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these calculations. For example, *survival* can be calculated as time to the development of hypertension, time to the development of a recurrence of cancer, or survival time free of treatment side effects. Furthermore, although we can look at a single survival curve, often the greatest interest lies in comparing two or more survival curves, such as for those who are treated and those who are not treated in a randomized trial. We may analyze treatment effectiveness by race/ethnicity to determine whether there are disparities in response to treatments. In conducting such comparisons, statistical methods are available to determine whether one curve is significantly different from another.

A third assumption is specific to traditional life tables, but not the Kaplan-Meier method, and deals with the use of predetermined intervals when calculating the life tables. The prime reason to use the traditional life table method over the Kaplan-Meier method is that if we are not able to identify the exact time of event, we must use an arbitrary interval within which the event took place. Subsequently we are not able to identify the exact time of withdrawals from the study. Thus, it is important to assume that there is a uniform distribution of risk and withdrawal during each time interval, and that there is no rapid change in the risk or withdrawal within a time interval. A reasonable way to achieve this assumption is to make the intervals as short as possible.

Example of Use of a Life Table

Traditional life tables are used in virtually every clinical area. However, they are less commonly used nowadays and have been replaced with the Kaplan-Meier method, in which the investigators are able to identify the exact time of event for each study participant. Life tables were the standard means by which survival is expressed and compared for a long time before the establishment of the Kaplan-Meier method. Let's examine a few examples. One of the great triumphs of pediatrics in recent decades has been the treatment of leukemia in children. However, the improvement has been much greater for White children than for Black children, and the reasons for this difference are not clear. At a time when survival rates from childhood acute leukemia were increasing rapidly, a study was conducted to explore the racial differences in survivorship. Figs. 6.15 to 6.17 show data from this study.[8] The curves are based on life tables that were constructed using the approach discussed earlier.

Fig. 6.15 shows survival for White and Black children with leukemia in Baltimore over a 16-year period. No Black children survived longer than 4 years, but some White children survived as long as 11 years in this 16-year period of observation.

What changes took place in survivorship during the 16 years of the study? Fig. 6.16 and Fig. 6.17 show changes in leukemia mortality over time in White and Black children, respectively. The 16-year period was divided into three periods: 1960 to 1964 *(solid line)*, 1965 to 1969 *(dashed line)*, and 1970 to 1975 *(dotted line)*.

In White children (see Fig. 6.16), survivorship increased in each successive period. For example, if we examine 3-year survival by looking at the 3-year point on each successive curve, we see that survival improved from 8% to 25% to 58%. In contrast, in Black children (see Fig. 6.17) there was much less improvement in survival over time; the curves for the two later 5-year periods almost overlap.

What accounts for this racial difference? First, we must take account of the small numbers involved and the possibility that the differences could have been due to chance. Let's assume, however, that the differences are real. During the the study period, tremendous strides

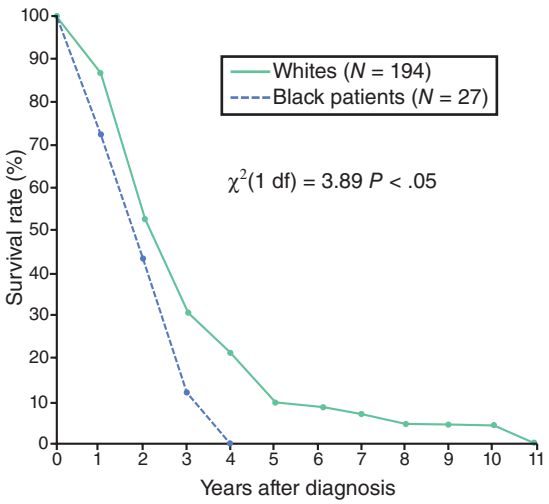

Fig. 6.15 Survival of children aged 0 to 19 years with acute lymphocytic leukemia by race, metropolitan Baltimore, 1960–1975. (From Szklo M, Gordis L, Tonascia J, Kaplan E. The changing survivorship of white and black children with leukemia. *Cancer.* 1978;42:59–66. Copyright 1978 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

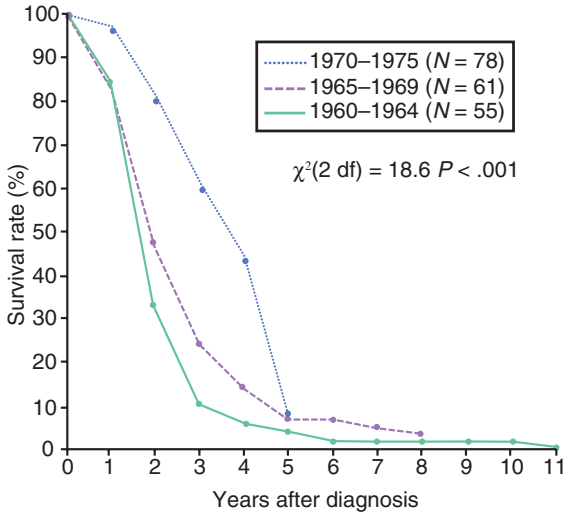

Fig. 6.16 Temporal changes in survival of White children aged 0 to 19 years with acute lymphocytic leukemia, metropolitan Baltimore, 1960–1975. (From Szklo M, Gordis L, Tonascia J, Kaplan E. The changing survivorship of white and black children with leukemia. *Cancer*. 1978;42:59–66. Copyright 1978 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

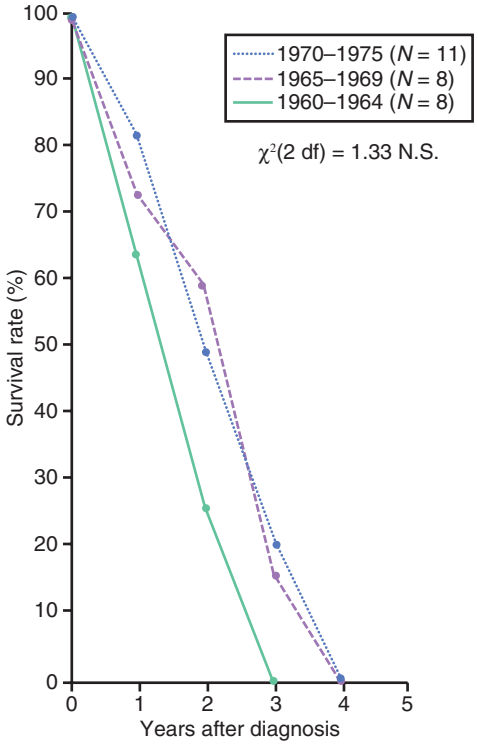

Fig. 6.17 Temporal changes in survival of Black children aged 0 to 19 years with acute lymphocytic leukemia, metropolitan Baltimore, 1960–1975. (From Szklo M, Gordis L, Tonascia J, Kaplan E. The changing survivorship of white and black children with leukemia. *Cancer*. 1978;42:59–66. Copyright 1978 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

occurred in the treatment of leukemia through combined therapy, including central nervous system radiation added to chemotherapy. Why, then, does a racial difference exist in survivorship? Why is it that the improvement in therapy that has been so effective in White children has not had a comparable benefit in Black children? Further analyses of the interval from the time the parent noticed symptoms to the time of diagnosis and treatment indicated that the differences in survival did not appear to be due to a delay in Black parents seeking or obtaining medical care. Because acute leukemia is more severe in Black people and more advanced at the time of diagnosis, the racial difference could reflect biologic differences in the disease, such as a more aggressive and rapidly progressive form of the illness. The definitive explanation is not known.

APPARENT EFFECTS ON PROGNOSIS OF IMPROVEMENTS IN DIAGNOSIS

We have discussed the assumption made in using a life table that no improvement in the effectiveness of treatment has occurred over calendar time during the period of the study. Another issue in calculating and interpreting survival rates is the possible effect of improvements in diagnostic methods over calendar time.

An interesting example was reported by Feinstein and colleagues.[9] They compared survival in a cohort of patients with lung cancer first treated in 1977 with survival in a cohort of patients with lung cancer treated from 1953 to 1964. Six-month survival was higher in the latter group for both the total group and for subgroups formed on the basis of stage of disease. The authors found that the apparent improvement in survival was due in part to *stage migration*, a phenomenon shown in Fig. 6.18A to C.

In Fig. 6.18A, patients with cancer are divided into "good" and "bad" stages, on the basis of whether they had detectable metastases in 1980. Some patients who would have been assigned to a "good" stage in 1980 may have had micro-metastases at that time, which would

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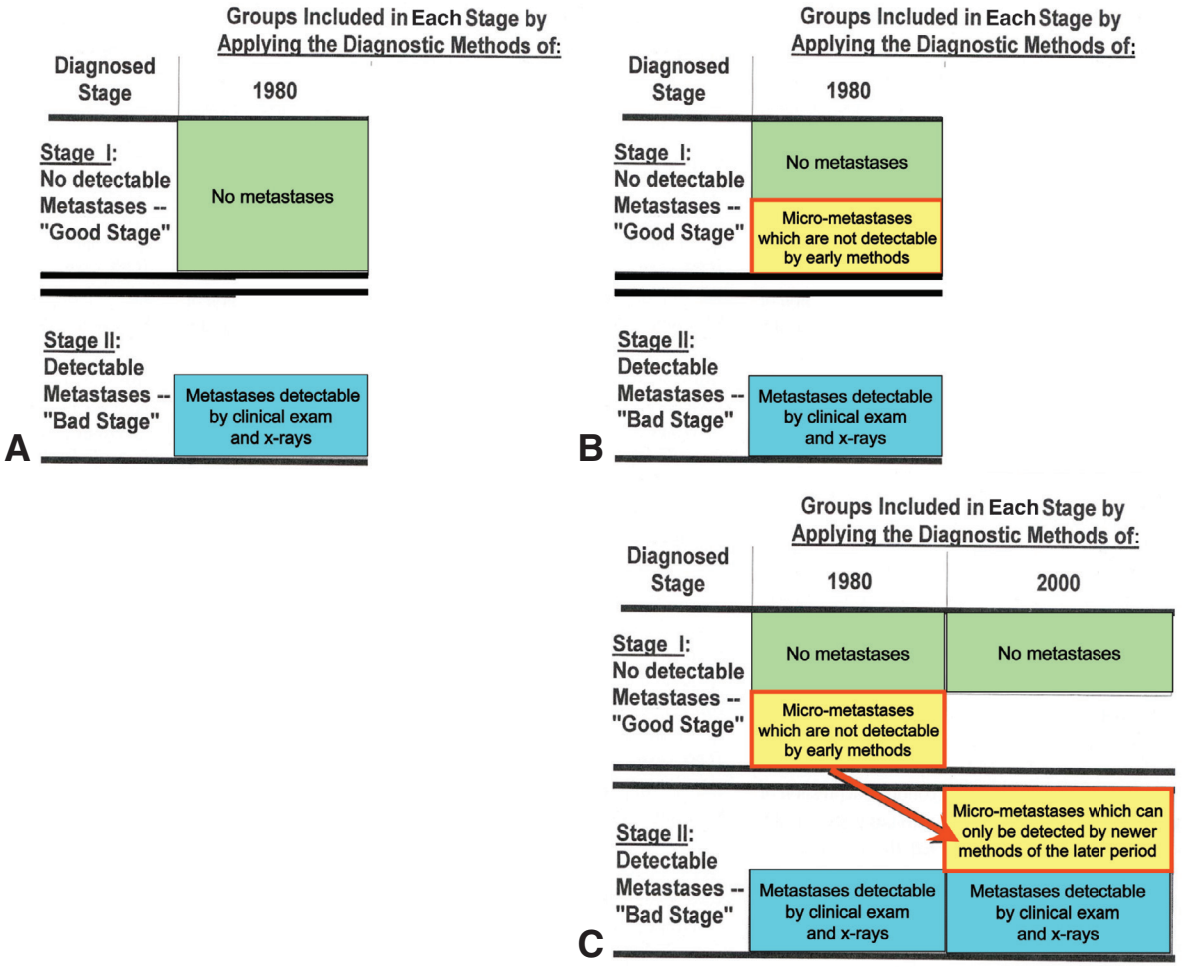

Fig. 6.18 Stage migration. **(A)** Classification of cases by presence or absence of detectable metastases in 1980. **(B)** Presence of undetectable micro-metastases in 1980. **(C)** Impact of improved diagnosis of micro-metastases in 2000 on classification of cases by presence or absence of detectable metastases.

have been unrecognized (see Fig. 6.18B). However, by 2000, as diagnostic technology improved, many of these patients would have been assigned to a "bad" stage, because their micro-metastases would now have been recognized using improved diagnostic technology that had become available (see Fig. 6.18C). If this had occurred, survival by stage would appear to have improved even if treatment had not become any more effective during this time.

Let's consider a hypothetical example that illustrates this effect of such stage migration. Fig. 6.19A to C show a hypothetical study of cancer case-fatality for 300 patients in two time periods, 1980 and 2000, *assuming no improvement in the effectiveness of available therapy between the two periods.* We will assume that as shown in Fig. 6.19A, in both time periods, the case-fatality is 10% for patients who have no metastases, 30% for those with micro-metastases, and 80% for those with metastases. Looking at Fig. 6.19B, we see that in 1980, 200 patients were classified as stage I. One hundred of these patients had no metastases, and 100 had unrecognized micro-metastases. Their case-fatalities were thus 10% and 30%, respectively. In 1980, 100 patients had clearly evident metastases and were classified as stage II; their case-fatality was 80%.

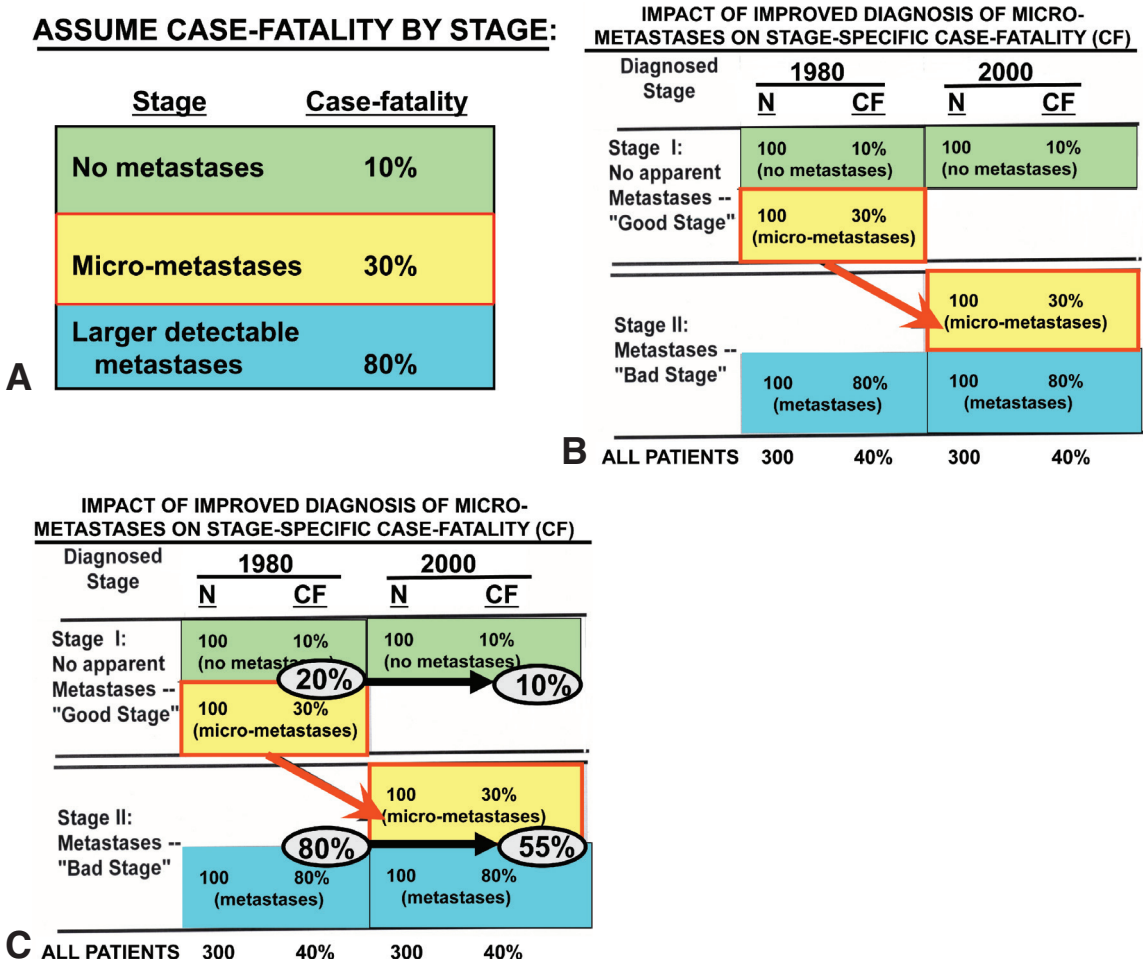

Fig. 6.19 Hypothetical example of stage migration. **(A)** Assumed case-fatality by stage. **(B)** Impact of improved diagnosis of micro-metastases on stage-specific case-fatality *(CF)*. **(C)** Apparent improvements in stage-specific survival as a result of stage migration even without any improvement in effectiveness of treatment.

As a result of improved diagnostic technology in 2000, micro-metastases were detected in the 100 affected patients, and these patients were classified as stage II (see Fig. 6.19C). Because the prognosis of the patients with micro-metastases is worse than that of the other patients in stage I, and because, in the later study period, patients with micro-metastases are no longer included in the stage I group (because they have migrated to stage II), the case-fatality for stage I patients appears to decline from 20% in the early period to 10% in the later period. However, although the prognosis of the patients who migrated from stage I to stage II was worse than that of the others in stage I, the prognosis for these patients was still better than that of the other patients in stage II, who had larger, more easily diagnosed metastases and a case-fatality of 80%. Consequently, the case-fatality for patients in stage II also appears to have improved, having declined from 80% in the early period to 55% in the later period, *even in the absence of any improvement in treatment effectiveness.*

The apparent improvements in survival in both stage I and stage II patients result only from the changed classification of patients with micro-metastases in the later period. Looking at the bottom line of the figure, we see that the case-fatality of 40% for all 300 patients has not changed from the early period to the later period. Only

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the apparent stage-specific case-fatalities have changed. It is therefore important to exclude the possibility of stage migration before attributing any apparent improvement in prognosis to improved effectiveness of medical care.

The authors call stage migration the *Will Rogers phenomenon*. The reference is to Will Rogers, an American humorist during the time of the economic depression of the 1930s. At that time, because of economic hardship, many residents of Oklahoma left the state and migrated to California. Rogers commented, "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

MEDIAN SURVIVAL TIME

Another approach to expressing prognosis is the median survival time, which is defined as the length of time that half (50%) of the study population survives. Why should we use median survival time rather than mean survival time, which is an average of the survival times? Median survival offers two advantages over mean survival. First, it is less affected by extremes, whereas the mean can be significantly affected by even a single outlier. One or two persons with a very long survival time could significantly affect the mean, even if all of the other survival times were much shorter. Second, if we used mean survival, we would have to observe all of the deaths in the study population before the mean could be calculated. However, to calculate median survival, we would only have to observe the deaths of half of the group under observation.

RELATIVE SURVIVAL

Let's consider 5-year survival for a group of 30-year-old men with colorectal cancer. What would we expect their 5-year survival to be if they did not have colorectal cancer? Clearly, it would be nearly 100%. Thus, we are comparing the survival observed in young men with colorectal cancer to a survival of almost 100% that is expected in those without colorectal cancer. What if we consider a group of 80-year-old men with colorectal cancer? We would not expect anything near 100% 5-year survival in a population of this age, even if they do not have colorectal cancer. We would want to compare the observed survival in 80-year-old men with colorectal cancer to the expected survival of 80-year-old men without colorectal cancer. For any group of people with a disease, we want to compare their survival to the survival we would expect in this age group even if they did not have the disease. This is known as the *relative survival*.

Relative survival is thus defined as the ratio of the observed survival to the expected survival:

$$\text{Relative survival} = \frac{\text{Observed survival in people with the disease}}{\text{Expected survival if disease were absent}}$$

Does relative survival really make any difference? Table 6.11 shows data for patients with cancer of the colon and rectum, both relative survival and observed survival from 1990 to 1998. When we look at the older age groups, which have high rates of mortality from other causes, there is a large difference between the observed and the relative survival. However, in young persons, who generally do not die of other causes, observed and relative survival for cancer of the colon and rectum do not differ significantly.

Another way to view relative survival is by examining the hypothetical 10-year survival curves of 80-year-old men shown in Fig. 6.20A to D. For reference, Fig. 6.20A shows a perfect survival of 100% (the horizontal line at the top) over the 10 years of the study period. Fig. 6.20B adds a curve of observed survival—that is, the actual survival observed in this group of patients with the disease over the 10-year period. As seen in Fig. 6.20C, the expected survival for this group of 80-year-old men is clearly less than 100% because deaths from other causes

TABLE 6.11 Five-Year Observed and Relative Survival (%) by Age for Colon and Rectum Cancer, 1990–1998: SEER Program, 1970–2011

Age (Year)	Observed Survival (%)	Relative Survival (%)
<50	64	65
50–64	61.9	65.4
65–74	54.3	62.9
>75	35.5	55.8

SEER, Surveillance, Epidemiology, and End Results (Study). Courtesy Dr. Louise Brinton and Mr. Jake Thistle of the National Cancer Institute, using the SEER Program, 1970–2011.

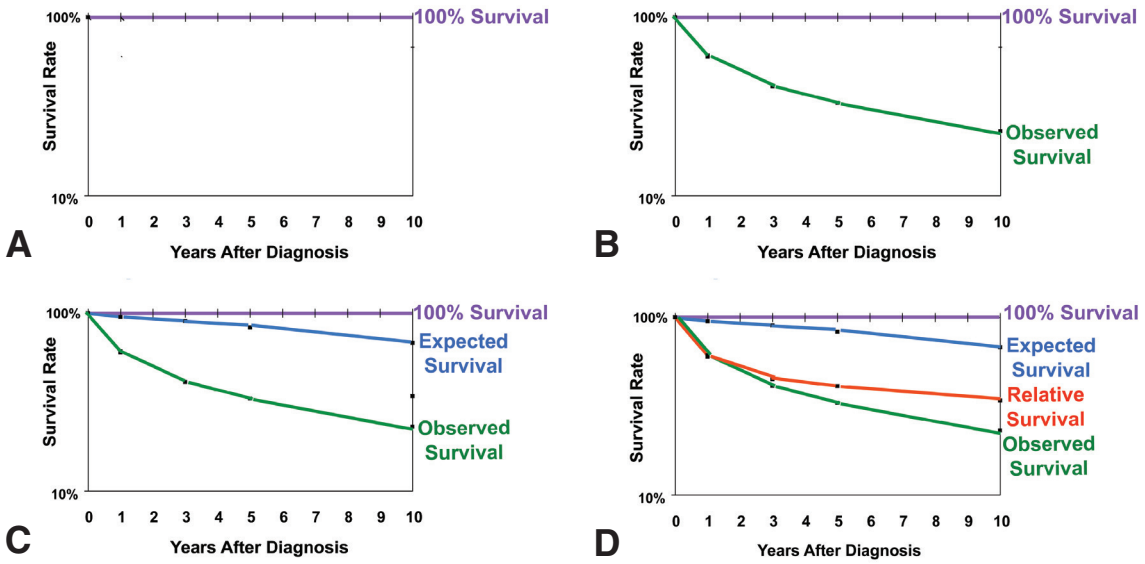

Fig. 6.20 Relative survival. **(A)** 100% survival over 10 years. **(B)** Observed survival. **(C)** Observed and expected survival. **(D)** Observed, expected, and relative survival.

are significant in this age group. The relative survival is the ratio of observed survival to expected survival. Since expected survival is less than perfect (100%) survival, and expected survival is the denominator for these calculations, the relative survival will be higher than the observed survival (see Fig. 6.20D).

GENERALIZABILITY OF SURVIVAL DATA

A final point in connection with the natural history and prognosis of disease is the question of which patients are selected for study. Let's look at one example.

Febrile seizures are common in infants. Children who are otherwise healthy often experience a seizure in association with high fever. The question arises as to whether these children should be treated with a regimen of phenobarbital or another long-term anticonvulsant medication. That is, is a febrile seizure a warning of subsequent epilepsy, or is it simply a phenomenon associated with fever in infants, in which case children are unlikely to have subsequent nonfebrile seizures?

To make a rational decision about treatment, the question we must ask is, "What is the risk that a child who has had a febrile seizure will have a subsequent nonfebrile seizure?" Fig. 6.21 shows the results of an analysis by Ellenberg and Nelson of published studies.[10]

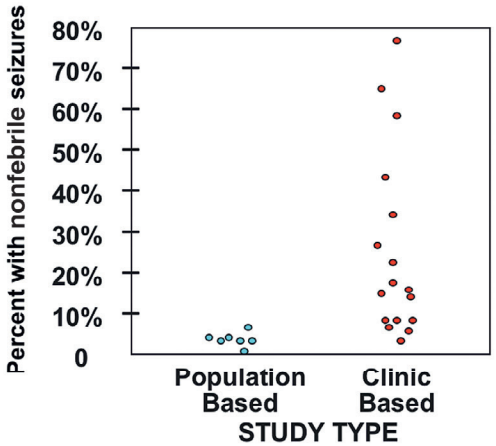

Fig. 6.21 Percentage of children who experienced nonfebrile seizures after one or more febrile seizures, by study design. (Modified from Ellenberg JH, Nelson KB. Sample selection and the natural history of disease: studies on febrile seizures. *JAMA*. 1980;243:1337–1340.)

Each dot shows the percentage of children with febrile seizures who later developed nonfebrile seizures in a different study. The authors divided the studies

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into two groups: population-based studies and studies based in individual clinics, such as epilepsy or pediatric clinics. The results from different clinic-based studies show a considerable range in the risk of later development of nonfebrile seizures. However, the results of population-based studies show little variation in risk, and the results of all these studies tend to cluster at a low level of risk.

Why should the two types of studies differ? Which results would you believe? Each of the clinics probably had different selection criteria and different referral patterns. Consequently, the different risks observed in the different clinic-based studies are probably the result of the selection of different populations in each of the clinics. In contrast, in the population-based studies (which may in fact be randomly selected), this type of variation due to selection is reduced or eliminated, which accounts for the close clustering of the data, and for the resultant finding that the risk of nonfebrile seizures is very low. The important point is that it may be very tempting to look at patient records in one hospital and generalize the findings to all patients in the general population. However, this is not a legitimate approach because patients who come to a certain clinic or hospital often are not representative of all patients in the community. This does not mean that studies conducted at a single hospital or clinic cannot be of value. Indeed, there is much to be learned from conducting studies at single hospitals. However, these studies are particularly prone to *selection bias*, and this possibility must always be kept in mind when the findings from such studies and their potential generalizability are being interpreted.

CONCLUSION

This chapter has discussed five ways of expressing prognosis (Box 6.3). Which approach is best depends on the research question being asked, the type of data that are available, data collection methods, and the purpose of the data analysis.

BOX 6.3 Five Approaches to Expressing Prognosis

1. Case-fatality
2. 5-year survival
3. Observed survival
4. Median survival time
5. Relative survival

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REVIEW QUESTIONS FOR CHAPTER 6

Question 1 is based on the information given in the table below:

Year of Treatment	No. of Patients Treated	NO. OF PATIENTS ALIVE ON EACH ANNIVERSARY OF BEGINNING TREATMENT		
		1st	2nd	3rd
2012	75	60	56	48
2014	63	55	31	
2015	42	37		
Total	180	152	87	48

A total of 180 patients were treated for disease X from 2012 to 2014, and their progress was followed to 2015. The treatment results are given in the table. No patients were lost to follow-up.

1. *What is the probability of surviving for 3 years?* _____

2. *An important assumption in this type of analysis is that:*
   - **a.** Treatment has improved during the period of the study
   - **b.** The quality of record-keeping has improved during the period of the study
   - **c.** No change has occurred in the effectiveness of the treatment during the period of the study
   - **d.** An equal number of men and women were enrolled each year
   - **e.** None of the above

3. *Which of the following is a good index of the severity of a short-term, acute disease?*
   - **a.** Cause-specific death rate
   - **b.** 5-year survival
   - **c.** Case-fatality
   - **d.** Standardized mortality ratio
   - **e.** None of the above

4. *A diagnostic test has been introduced that will detect a certain disease 1 year earlier than it is usually detected. Which of the following is most likely to happen to the disease within the 10 years after the test is introduced? (Assume that early detection has no effect on the natural history of the disease. Also assume that no changes in death certification practices occur during the 10 years.)*
   - **a.** The period prevalence rate will decrease
   - **b.** The apparent 5-year survival will increase
   - **c.** The age-adjusted mortality rate will decrease
   - **d.** The age-adjusted mortality rate will increase
   - **e.** The incidence rate will decrease

5. *Which of the following statements about relative survival is true?*
   - **a.** It refers to survival of first-degree relatives
   - **b.** It is generally closer to observed survival in elderly populations
   - **c.** It is generally closer to observed survival in young populations
   - **d.** It generally differs from observed survival by a constant amount, regardless of age
   - **e.** None of the above

Questions 6 to 8 are based on the data in the table below. The data were obtained from a study of 248 patients with acquired immunodeficiency syndrome (AIDS) who were given a new treatment and followed to determine survival. The study population was followed for 36 months.

Note: Carry your calculations in the table to four decimal places (i.e., 0.1234), but give the final answer to three decimal places (e.g., 0.123 or 12.3%).

6. *For those people who survived the second year, what is the probability of dying in the third year?* _____

7. *What is the probability that a person enrolled in the study will survive to the end of the third year?* _____

Survival of Patients With Acquired Immunodeficiency Syndrome After Diagnosis

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(1) Interval Since Beginning Treatment (Months)	(2) Alive at Beginning of Interval	(3) Died During Interval	(4) Withdrew During Interval	(5) Effective Number Exposed to Risk of Dying During Interval: Col (2) $-\frac{1}{2}$ [Col (4)]	(6) Proportion Who Died During Interval: $\frac{\text{Col (3)}}{\text{Col (5)}}$	(7) Proportion Who Did Not Die During Interval: 1 − Col (6)	(8) Cumulative Proportion Who Survived From Enrollment to End of Interval: Cumulative Survival
x	l_x	d_x	w_x	l'_x	q_x	p_x	P_x
1–12	248	96	27				
13–24	125	55	13				
25–36	57	55	2				

8. *Before reporting the results of this survival analysis, the investigators compared the baseline characteristics of the 42 persons who withdrew from the study before its end with those of the participants who had complete follow-up. This was done for which of the following reasons:*

a. To test whether randomization was successful

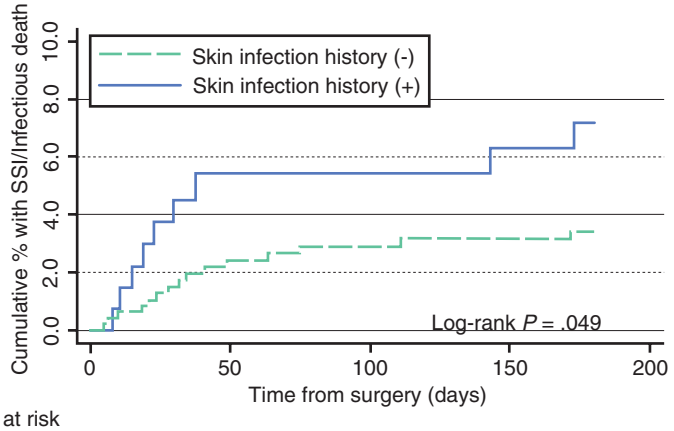
b. To check for changes in prognosis over time

c. To check whether those who remained in the study represent the total study population

d. To determine whether the outcome of those who remained in the study is the same as the outcome of the underlying population

e. To check for confounders in the exposed and nonexposed groups

9. *This question is based on a study by Faraday et al. where they examined the association between history of skin infection and surgical site infection (SSI) after elective surgery. They followed 613 patients for about 6 months. The figure below shows the Kaplan-Meier estimates of cumulative incidence of SSI or infectious death by history of skin infection. Using the figure, the survival time for those with a cumulative skin infection history (+)* of approximately 5.0% is:



(Faraday N, Rock P, Lin EE, et al. Past history of skin infection and risk of SSI after elective surgery. *Ann Surg.* 2013;257:150–154.)

a. 30–50 days
b. 60–80 days
c. 90–110 days
d. 120–130 days
e. Information cannot be obtained from this figure

10. *In the Faraday study (see question 9), which of the following is/are necessary assumption(s) when using the Kaplan-Meier method to estimate cumulative incidence:*

a. The incidence of SSI events is less than 10% in the study population
b. Those who are lost to follow-up before 6 months have the same survival experience as those who remain in the study
c. Events and loss to follow-up occur at a constant rate during each time interval
d. Those who are censored prior to 6 months are more likely to develop SSI than those who are not censored prior to 6 months

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SECTION II

Using Epidemiology to Identify the Cause of Disease

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7

Observational Studies

LEARNING OBJECTIVES

- To describe the motivations for and the design, of observational studies.
- To discuss early origins of the research question, including case reports, case series, and ecologic studies.
- To describe the cross-sectional study design and its importance.
- To discuss case-control studies, including selection of cases and controls.
- To discuss potential selection biases in case-control studies.
- To discuss information biases in case-control studies, including limitations in recall and recall bias.
- To describe other issues in case-control studies, including matching and the use of multiple controls.
- To introduce the case cross-over study design.

CASE REPORTS AND CASE SERIES

Perhaps one of the most common and early origins of medical research questions is through careful observations by physicians and other health care providers of what they see during their routine clinical practice. Such individual-level observations can be documented in a case report, describing a particular clinical phenomenon in a single patient, or in a case series that describes more than one patient with similar problems. The 2022 Monkeypox transmission outside of Central and West Africa is a good case (referred to by the WHO as mpox as of 2023). Both case reports and case series are considered the simplest of study designs (although some assert that they are merely "prestudy designs"). The main objective of case reports and case series is to document a comprehensive and detailed description of the case(s) under observation. This allows other physicians to identify and potentially report similar cases from their practice, especially when they share geographic or specific clinical characteristics. For example, in late 2019, an outbreak of a novel coronavirus was reported in Wuhan, China, which spread rapidly around the world. The first case of 2019 novel coronavirus disease (COVID-19) was documented as a case report in January 2020.[1] It described the method by which this case was identified, how it was diagnosed, and the clinical course and management of the patient. Following this report, numerous case reports and case series of patients diagnosed with COVID-19 were reported, with the primary objective of describing the diagnosis and management in different patient populations, e.g., elderly, children, pregnant women, patients undergoing dialysis, healthcare workers, etc.

Despite the fact that case reports and case series are merely descriptive in nature with no reference group to make a strict comparison, the totality of the clinical experience that the world accumulated over the weeks and months of the rapidly evolving (and changing) pandemic dynamics was instrumental in the development of the Centers for Disease Control and Prevention (CDC)'s guidelines[2] (Fig. 7.1) for the isolation of a child in an early care and education program who might have Zika and quarantine of individuals who are either positive with COVID-19 or were in close contact with someone who is, respectively.

Case reports and case series are key hypothesis-generating tools, especially when they are simple,

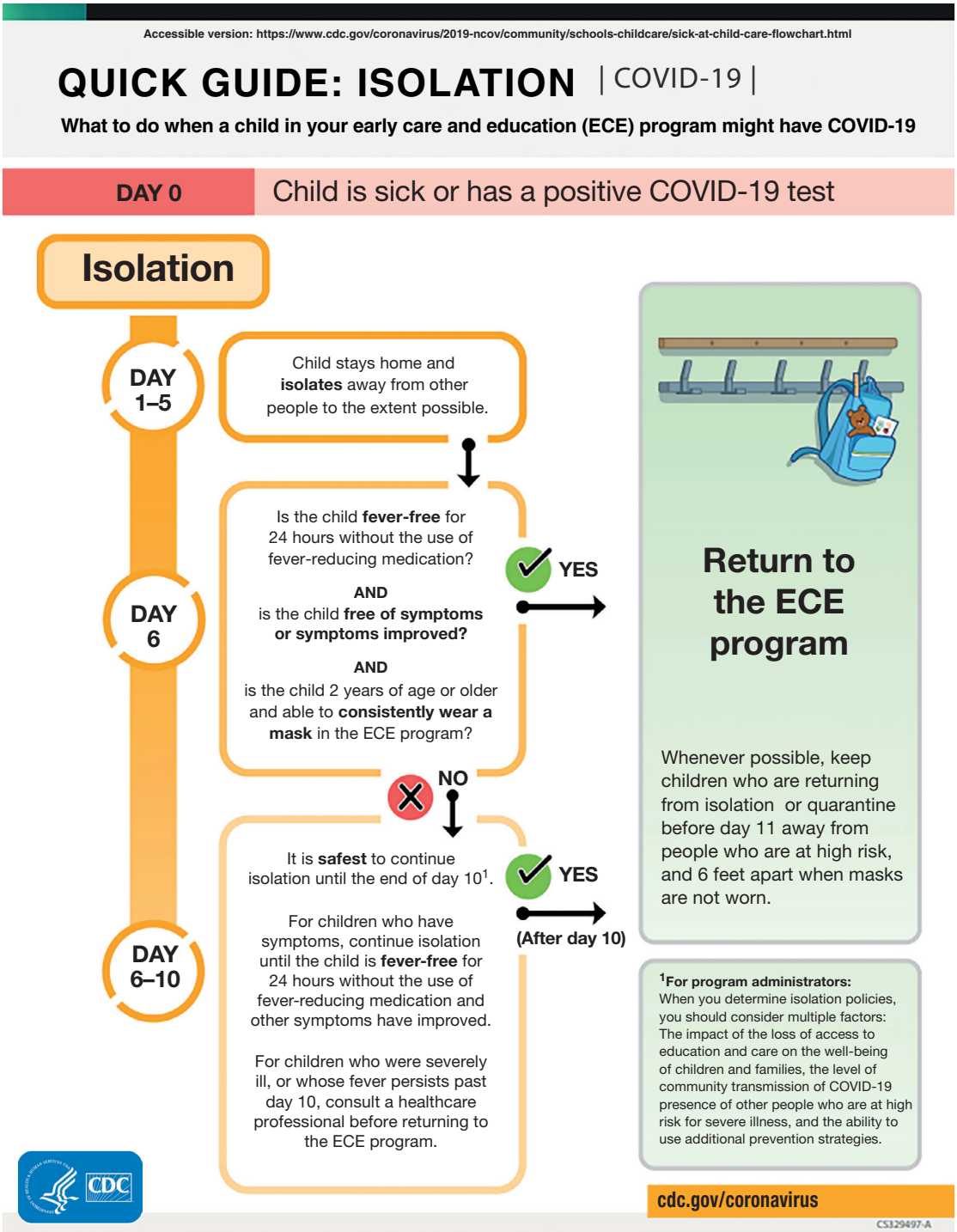

Fig. 7.1 Example of guidance from CDC on what to do when a child in your early care and education (ECE) program might have COVID-19. (From National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention.) https://www.cdc.gov/earlycare/pdf/329497-A_ECE_Isolation_SEPT-23-508.pdf.

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inexpensive, and easy to conduct in the course of busy clinical settings. However, the lack of a comparison group is a major disadvantage. Furthermore, external validity (generalizability) is limited, given the possibly biased selection of cases (all identified in clinical practice). The data presented in case reports and case series are primarily collected for the purpose of clinical care and not for research, and are dependent on physician interpretation. Finally, any association observed in a case report or a case series is prone to potentially unmeasured confounding unbeknown to the investigators. We will talk more about these issues when we discuss the threats to internal validity of research studies.

ECOLOGIC STUDIES

The first approach in determining whether an association exists may be a study of group characteristics, the so-called *ecologic study*. In 2020, early in the COVID-19 pandemic, an ecologic study was conducted in which the authors collected data from 173 countries on bacillus Calmette-Guérin (BCG) vaccination coverage/policies and COVID-19 risk, positivity, and clinical outcomes, e.g., mortality.[3] Fig. 7.2 shows the correlation of each country's BCG vaccination coverage and mortality from COVID-19 per million population. The authors concluded that the presence of a national BCG vaccination program and the high BCG vaccination coverage are inversely associated with COVID-19 mortality. What is the problem with drawing such a conclusion from this type of study? The problem is that we do not know whether the *individuals* who died from COVID-19 in each country actually had a BCG vaccination. All we have are country-wide binary variables of presence of a national BCG vaccination program, and the national *average* of BCG vaccination coverage.

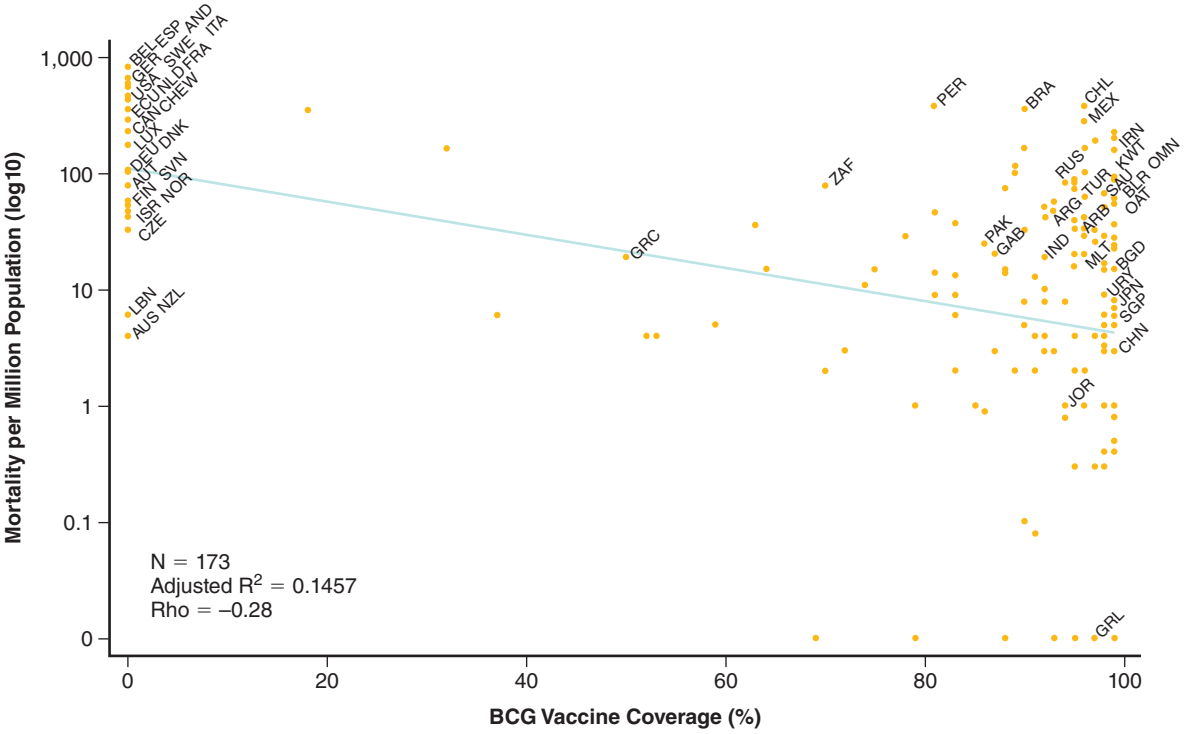

Fig. 7.2 Scatter plot showing the association between COVID-19-related mortality and BCG vaccine coverage. Mortalities per million population on 17 July 2020 are transformed to the common logarithm (log10) in the graph. Since the variable of "BCG vaccine coverage" showed a non-normal distribution, Spearman's rank correlation was applied to calculate rho, to quantify the strength of the association. Selected country names are shown using three-letter country codes.

No account is taken of variability between individuals in that country with regard to BCG vaccination. This problem is called the *ecologic fallacy*—we may be ascribing to members of a group some characteristic that they in fact do not possess as individuals. This problem arises in an ecologic study because data are only available for groups; we do not have exposure and outcome data for each person in the population. The hypothesis of the association between BCG vaccination and COVID-19 clinical outcomes was later dismissed by further research.

Table 7.1 shows data from a study in Northern California exploring a possible relation between prenatal exposure to influenza during an influenza outbreak and the later development of acute lymphocytic leukemia in a child.[4] The table shows incidence data for children who were not in utero during a flu outbreak and for children who were in utero in the first, second, or third trimester of the pregnancy during the outbreak. Below these figures, the data are presented as relative risks, with the risk being set at 1.0 for those who were not in utero during the outbreak (this is the reference or comparison group) and the other rates being set relative to this. The data indicate a high relative risk for leukemia in children who were in utero during the flu outbreak in the first trimester.

What is the problem? The authors themselves stated, "*The observed association is between pregnancy during an influenza epidemic and subsequent leukemia in the offspring of that pregnancy. It is not known if the mothers of any of these children actually had influenza during their pregnancy*."[4] What we are missing are *individual data* on exposure (influenza infection). One might ask, why didn't the investigators obtain the necessary exposure data? The likely reason is that the investigators used birth certificates and data from a cancer registry; both sources of data are relatively easy to obtain. This approach did not require follow-up of the children and direct contact with individual subjects. If we are impressed by these ecologic data, we might want to carry out a study specifically designed to explore the possible relationship of prenatal flu and leukemia. However, such a study would probably be logistically considerably more difficult and more expensive to conduct.

In view of these problems, are ecologic studies of value? Yes, they can suggest avenues of research that may be promising in casting light on etiologic relationships, a setting that can be considered as *hypothesis-generating*. In and of themselves, however, they do not demonstrate conclusively that a true association exists.

For many years, legitimate concerns about the possibility of ecologic fallacy gave ecologic studies a bad name and diverted attention from the importance of studying potentially meaningful relationships that can be only studied ecologically, such as those between the individual and the community in which he or she lives. For example, Rose and associates[5] studied the relationship of socioeconomic and racial characteristics of a neighborhood and the receipt of angiography in a community-based sample of residents who had had a myocardial infarction (MI). Among the 9,941 people with MI participating in the Atherosclerosis Risk in Communities Study, compared to White residents from high neighborhood-level income areas, Black residents from low and medium neighborhood-level income areas as well as White residents from low neighborhood-level income areas were less likely to be subjected to an angiographic examination. On the other hand, Black residents from high neighborhood-level income areas and White residents from medium neighborhood-level income areas were not disadvantaged with respect to receiving angiography. Thus, future studies addressing both individual risk factors and ecologic risk factors, such as neighborhood characteristics, and the possible interactions of both types of factors may improve our understanding of access to an angiographic examination.

Another example of the importance of ecologic data is given by schistosomiasis, a disease caused by a freshwater parasite, *Schistosoma mansoni*, that can affect the genitourinary or gastrointestinal tracts as well as the central nervous systems, and it is also a risk factor for bladder and liver cancer. Individuals are exposed through contact with infested water. Those in rural communities are at highest risk for contracting schistosomiasis; exposure may come from agriculture or fishing populations, women washing clothes, or children playing in infested water. Egypt has the highest endemic worldwide prevalence of schistosomiasis, dating back to its dynastic period.[6] Parenteral antischistosomal therapy (PAT) use with potassium antimony tartrate, commonly called tartar emetic, has been used for mass-treatment in Egypt since the 1920s through 12 weekly intravenous injections.

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TABLE 7.1 Average Annual Crude Incidence Rates and Relative Risks of Acute Lymphocytic Leukemia by Cohort and Trimester of Flu Exposure for Children Younger Than 5 Years, San Francisco/Oakland (1969–1973)

		FLU EXPOSURE			
		TRIMESTER			
	No Flu Exposure	1st	2nd	3rd	Total
Incidence rates per 100,000	3.19	10.32	8.21	2.99	6.94
Relative risks	1.0	3.2	2.6	0.9	2.2

Modified from Austin DF, Karp S, Dworsky R, et al. Excess leukemia in cohorts of children born following influenza epidemics. *Am J Epidemiol*. 1977;10:77-83.

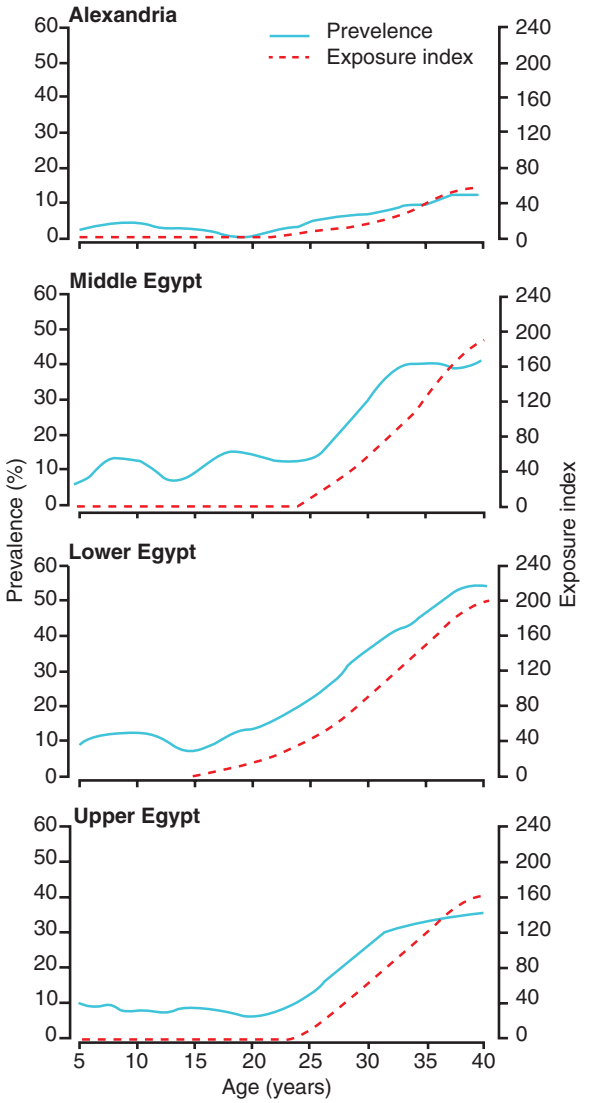

Fig. 7.3 Comparison of hepatitis C virus prevalence and exposure index by cohort and region. (Reprinted with permission from Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet*. 2000;11;355:887-891.)

These injections are done with reusable glass syringes generally without proper sterilization procedures, which may have been responsible for Egypt also having the highest hepatitis C prevalence in the world.[7] (Tartar emetic was the only treatment for schistosomiasis until praziquantel [Biltricide], a highly effective oral treatment, was introduced in the 1980s.) In 2000, Frank et al.[8] studied the ecologic association in Egypt governorate areas between annual PAT use with tartar emetic and the seroprevalence of antibodies to hepatitis C virus (HCV) in 8499 Egyptians aged 10 to 50 years. Overall, age-adjusted prevalence of antibodies to HCV was found to be 21.9%. Fig. 7.3 shows the association between region-specific prevalence of antibodies to HCV with region-specific PAT exposure, which suggests that the variation in seroprevalence of antibodies to HCV between regions may be explained by PAT exposure (odds ratio 1.31 [95% confidence interval {CI}: 1.08−1.59]; $P = .007$). To date, the massive HCV transmission through PAT use in Egypt is considered the largest iatrogenic transmission of a bloodborne pathogen ever recorded. Most recently, the Egyptian Ministry of Health and Population launched a national campaign "*100 Million Healthy Lives*" to screen for HCV in the general adult population in Egypt to accurately estimate the burden and distribution of HCV.[9] Of 49.6 million adult Egyptians who participated in the screening program, the prevalence of HCV seropositives in Egypt was estimated to be 4.6% (95% CI: 4.6–4.6). Fig. 7.4 shows a map of the HCV seropositive population in the Egyptian governorates. HCV-positive patients who were identified through this campaign were offered free treatment of a recently FDA-approved antiviral

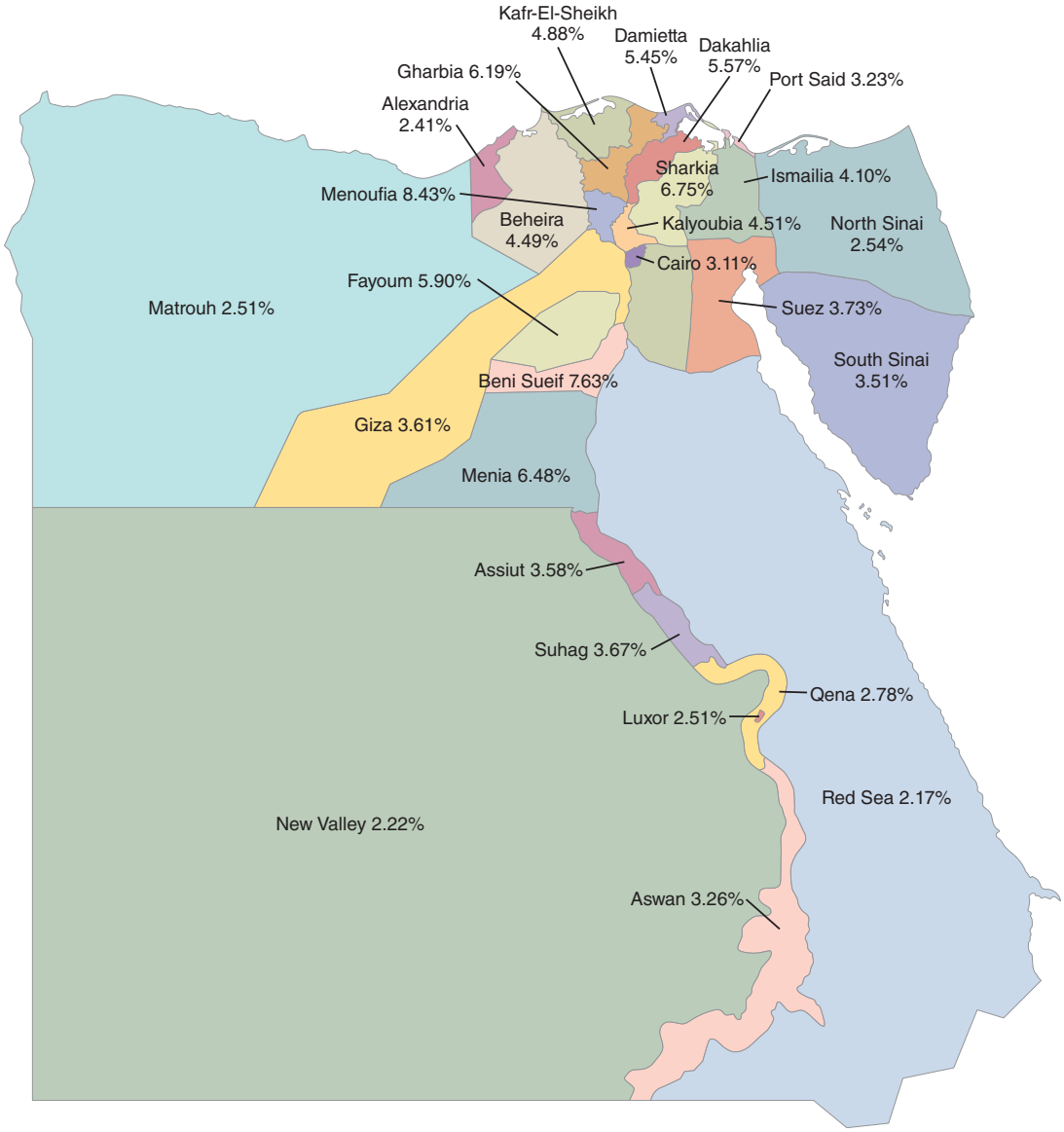

Fig. 7.4 A heat map of the Arab Republic of Egypt showing the proportion of Egyptian adults who are HCV seropositive among those who have been screened for HCV antibodies in the *"100 Million Healthy Lives"* national campaign in Egypt in 2020. (https://www.nejm.org/doi/full/10.1056/NEJMsr1912628.)

medication to eliminate HCV infection. Nearly one million adults who were HCV seropositive were offered the treatment and 65% completed the treatment regimen. Of these, 68% completed a 12-week follow up after treatment and 99% of them showed sustained virologic response.

It has been claimed that because epidemiologists generally show tabulated data and refer to characteristics of groups, the data in all epidemiologic studies are group data. This is not true. In cross-sectional, case-control, cohort studies and randomized trials, data on exposure and disease outcome are available for every individual in

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the study (although we must account for some missing data), even though these data are commonly grouped in tables and figures. On the other hand, only grouped data are available in ecologic studies, such as, for example, country-by-country data on average salt consumption and average systolic blood pressure.

Interestingly, when variability of an exposure is limited, ecologic correlations may provide a more valid answer on the presence of an association than studies based on individuals. Wynder and Stellman have summarized this phenomenon as follows: "*If cases and controls are drawn from a population in which the range of exposures is narrow, then a study may yield little information about potential health effects.*"[10]

CROSS-SECTIONAL STUDIES

Another common study design used in initially investigating the association between a specific exposure and a disease of interest is the *cross-sectional study.* Let's assume that we are interested in the possible relationship of increased serum cholesterol level (the *exposure*) to electrocardiographic (ECG) evidence of coronary heart disease (CHD, the *disease* or the *outcome*). We survey a population, and for each participant, we determine the serum cholesterol level and perform an ECG for evidence of CHD. The presence of CHD defines a prevalent case. This type of study design is called a *cross-sectional study* because both exposure and disease outcome are determined *simultaneously* for each study participant; it is as if we were viewing a snapshot of the population at a certain point in time. Another way to describe a cross-sectional study is to imagine that we have sliced through the population, capturing levels of cholesterol *and* evidence of CHD at the same time. Note that in this type of approach, the cases of disease that we identify are *prevalent* cases of the disease in question (which is the reason why a cross-sectional study is also called a "prevalence study"), because we know that they existed at the time of the study, but we do not know their duration (the interval between the onset of the disease and "today"), or whether the exposure happened before the outcome. The impossibility of determining a temporal sequence "exposure-disease" may result in temporal bias when it is the disease that causes the exposure. For example, prevalent cases of CHD may engage in leisure physical activity more often than healthy subjects (and thus a lower prevalence of physical inactivity), as the occurrence of an acute episode of CHD may prompt physicians to recommend physical exercise to their CHD patients, a phenomenon that is also known as "*reverse causality*." (Note, however, that when information on exposure is obtained by a questionnaire, it is possible to find out whether a given exposure [e.g., sedentary habits, smoking, or excessive alcohol drinking] was present prior to the disease onset, thus allowing the identification of the temporal sequence between the exposure and the disease.)

In addition to temporal bias, *selection bias* may also occur in a cross-sectional study when the exposure is related to the duration of the disease; thus, for example, if exposure-induced incident cases have a shorter survival than unexposed incident cases, prevalent cases, which are by definition survivors, may have a lower proportion of past exposure than those that would have been observed if incident cases had been included in the study. In other words, identifying only prevalent cases would exclude those who died sooner after the disease developed but before the study was carried out. For example, we know that a high serum cholesterol level causes CHD. However, when doing a cross-sectional study, the observed association may be a function of both the risk of *developing* CHD and with *survival* after CHD onset.

Another example of *survival bias* is given by smoking-induced lung emphysema. Smoking not only causes emphysema, but in addition, survival of patients with smoking-induced emphysema is worse than that of patients whose emphysema results from other causes (e.g., asthma or chronic bronchitis). As a result, past smoking will be observed less frequently in prevalent than in incident cases of emphysema. This type of survival bias is also known as *prevalence-incidence bias*.

In view of its biases, the results of a cross-sectional study should be used to generate hypotheses that can then be evaluated using a study design that includes the identification of incident cases and allows establishing the temporal sequence of the exposure and the outcome. Nevertheless, cross-sectional studies, like political polls and sample surveys, are widely used and are often the first studies conducted before moving on to more advanced (and valid) study designs.

The general design of a cross-sectional (or prevalence) study is seen in Fig. 7.5. We define a population and determine the presence or absence of exposure and

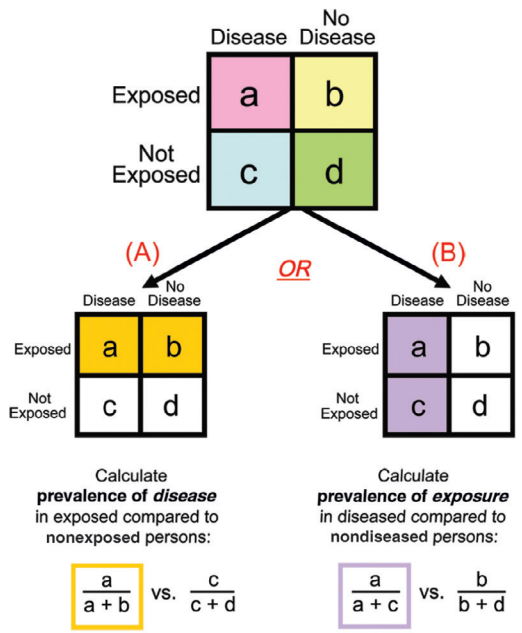

Fig. 7.5 Design of a hypothetical cross-sectional study. *(top)* A 2 × 2 table of the findings from the study; *(bottom)* two possible approaches to the analysis of results: **(A)** Calculate the prevalence of disease in exposed persons compared to the prevalence of disease in nonexposed persons, *or* **(B)** Calculate the prevalence of exposure in persons with disease compared to the prevalence of exposure in persons without disease.

the presence or absence of disease (or any other *health outcome of interest*) for each individual at the same time. Each subject then can be categorized into one of four possible subgroups. Of course, it may take months to conduct the prevalence study, so we have to assume that there is no temporal change in the exposure and disease association.

As seen in the 2 × 2 table in the top portion of Fig. 7.5, there will be *a* persons, who have been exposed and have the disease; *b* persons, who have been exposed but do not have the disease; *c* persons, who have the disease but have not been exposed; and *d* persons, who have neither been exposed nor have the disease. It is important to highlight the valuable information we can obtain from a 2 × 2 table (or an n × n table) as a simple and easy way to summarize data from any research study.

To determine whether there is evidence of an association between exposure and disease from a cross-sectional study, we have a choice between two possible approaches, which in Fig. 7.5 are referred to as (A) and (B). If we use (A), we can calculate the prevalence of disease in persons with the exposure $\left(\frac{a}{a+b}\right)$ and compare it with the prevalence of disease in persons without the exposure $\left(\frac{c}{c+d}\right)$. If we use (B), we can compare the prevalence of exposure in persons with the disease $\left(\frac{a}{a+c}\right)$ to the prevalence of exposure in persons without the disease $\left(\frac{b}{b+d}\right)$. The details of both approaches are shown in the bottom portion of Fig. 7.5.

If we determine in such a study that there appears to be an association between increased cholesterol level and CHD, we are left with several issues to consider. First, in this cross-sectional study, we are identifying prevalent (existing) cases of CHD rather than incident (new) cases; such prevalent cases may not be representative of all cases of CHD that have developed in this population. For example, identifying only prevalent cases would exclude those who died after the disease developed but before the study was carried out. Therefore, even if an association of exposure and disease is observed, the association may be with *survival* after CHD rather than with the risk of *developing* CHD. Second, because the presence or absence of both exposure and disease was determined *at the same time* in each participant in the study, it is often not possible to establish a temporal relationship between the exposure and the onset of disease. Thus, in the example given at the beginning of this section, it is not possible to tell whether or not the increased cholesterol level *preceded* the development of CHD. Without information on temporal relationships, it is conceivable that the increased cholesterol level could have occurred as a result of the CHD, in which case we call it "*reverse causality*", or perhaps both may have occurred as a result of another factor. If it turns out that the exposure did not precede the development of the disease, the association cannot reflect a causal relationship. (The cholesterol example is merely hypothetical, as we know for sure that a high concentration of cholesterol is a risk factor for CHD and, thus, by definition precedes the disease.)

Farag et al. used data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey of the noninstitutionalized US civilian population, to examine a

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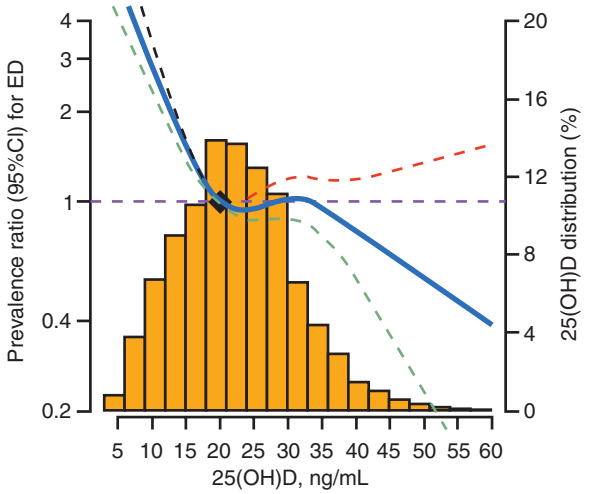

Fig. 7.6 Restricted cubic spline of 25(OH)D and adjusted prevalence ratio of erectile dysfunction *(ED)*, NHANES 2001–04. Curves represent adjusted prevalence ratio *(solid line)* and the 95% confidence intervals *(dashed lines)* based on restricted cubic splines for 25(OH)D level with knots at 10, 20, 30, and 40 ng/mL. The reference values were set at 20 ng/mL. Model is adjusted for age, race, smoking, alcohol consumption, body mass index, physical activity, hypertension, diabetes, hypercholesterolemia, estimated glomerular filtration rate, C-reactive protein, and the use of antidepressants and beta blockers. (From Farag YM, Guallar E, Zhao D, et al. Vitamin D deficiency is independently associated with greater prevalence of erectile dysfunction: the National Health and Nutrition Examination Survey (NHANES) 2001–2004. *Atherosclerosis.* 2016;252:61-67.)

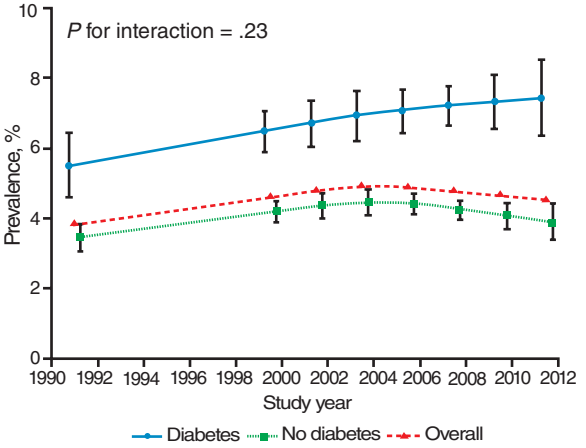

Fig. 7.7 Adjusted prevalence of stage 3 and 4 chronic kidney disease (estimated glomerular filtration rate of 15 to 59 mL/min/1.73 m^2 calculated with Chronic Kidney Disease Epidemiology Collaboration equation) in US adults, NHANES 1988–1994 through 2011–2012. (From Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med.* 2016;165:473-481.)

potential association between vitamin D and erectile dysfunction in men who were free from cardiovascular disease.[11] A dose-response (graded) relationship was found between vitamin D deficiency and erectile dysfunction (prevalence ratio 1.30, 95% CI: 1.08−1.57; Fig. 7.6). Notwithstanding the biases inherent to the cross-sectional design, the study's findings suggest the need to evaluate the association of vitamin D deficiency with erectile function using more sophisticated study designs.

Serial cross-sectional studies are also useful to evaluate trends in disease prevalence over time to inform health care policy and planning. Murphy and colleagues used annual NHANES data, yearly from 1988 to 1994 and every 2 years from 1999 to 2012, to examine trends in chronic kidney disease (CKD) prevalence.[12] Fig. 7.7 shows the temporal trends in adjusted prevalence of stages 3 and 4 CKD from NHANES 1988–94 through 2011–12, categorized by presence or absence of diabetes. As shown in the figure, there was an initial increase in adjusted prevalence of stages 3 and 4 CKD that leveled off in the early 2000s among nondiabetic individuals but continued to increase in diabetic individuals.

To minimize health research costs, researchers often depend on self-reported data. Weight and height are the most common self-reported variables. However, self-reports are prone to under- or overreporting. Cross-sectional data can help validate and correct errors in self-reported weight and height. For example, Jain compared self-reported with measured cross-sectional weight and height data from the NHANES for the period 1999–2006. This comparison allowed him to estimate a correction factor, which was then applied to the prevalence of obesity based on self-reported weight and height obtained from the CDC's Behavioral Risk Factor Surveillance System conducted by the states. Jain estimated that the weight/height self-reporting bias resulted in an approximately 5% lower obesity prevalence in both men and women than was actually measured.[13]

CASE-CONTROL STUDIES

Suppose you are a clinician and you have seen a few patients with a certain disease. You observe that many of

them have been exposed to a particular agent—biological or chemical. You hypothesize that their exposure is related to their risk of developing this disease. How would you go about confirming or refuting your hypothesis?

Let's consider a real-life example:

> *It was long thought that hyperacidity is the cause of peptic ulcer disease (PUD). In 1982, Australian physicians Barry Marshall and Robin Warren discovered Helicobacter pylori (H. pylori) in the stomachs of PUD patients and showed that H. pylori is able to adapt to the acidic environment of the stomach. However, their observations were not enough to establish the causal association between H. pylori and PUD. Subsequently, they suggested that antibiotics, not antacids, are the effective treatments for PUD, a suggestion that was heavily criticized at that time. It was not until 1994 when the National Institutes of Health came to a consensus expert opinion based on the available evidence that detection and eradication of H. pylori are key in the treatment of PUD. Drs. Marshall and Warren were awarded the Nobel Prize in Physiology or Medicine in 2005.*[14]

To determine the significance of clinical observations in a group of cases reported by physicians, a comparison (sometimes called a control or reference) group is needed. Observations based on case series would have been intriguing, but no firm conclusion would be possible without comparing these observations in cases to those from a series of controls who are similar in most respects to the cases but are free of the disease under study. Comparison is an essential component of epidemiologic investigation and is well exemplified by the case-control study design. Comparison is the essence of research!

Design of a Case-Control Study

Fig. 7.8 shows the design of a *case-control study.* To examine the possible relation of an exposure to a certain disease, we identify a group of individuals with that disease (called *cases*) and, for purposes of comparison, a group of people without that disease (called *controls or non-cases; this is why this design used to be called "case-non-case study"*). We then determine what proportion of the cases was exposed and what proportion was not. We also determine what proportion of the controls was exposed and what proportion was not. In the example of children with cataracts, the cases would consist of children with cataracts, and the controls would consist of children without cataracts. For each child, it would then be necessary to ascertain whether or not the mother was exposed to rubella during her pregnancy with that child. We anticipate that if the exposure (rubella) is in fact related to the disease (cataracts), the prevalence of history of exposure among the cases (children with cataracts) will be greater than that among the controls (children with no cataracts). Thus in a case-control study, if there is an association of an exposure with a disease, the prevalence of history of exposure should be higher in persons who have the disease (cases) than in those who do not have the disease (controls).

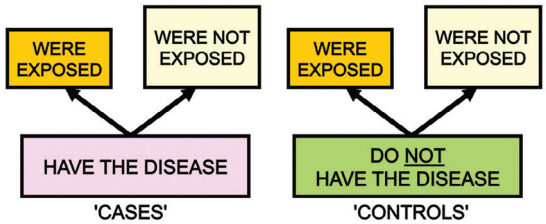

Fig. 7.8 Design of a case-control study.

TABLE 7.2 Design of Case-Control Studies

	FIRST, SELECT: Cases (With Disease)	Controls (Without Disease)
Then, Measure Past Exposure:		
Were exposed	a	b
Were not exposed	c	d
Totals	$a + c$	$b + d$
Proportions who were exposed	$\left(\frac{a}{a+c}\right)$	$\left(\frac{b}{b+d}\right)$

Table 7.2 presents a hypothetical schema of how a case-control study is conducted. We begin by selecting cases (with the disease) and controls (without the disease), and then measure past exposure by interview or by review of medical or employee records. If the exposure is dichotomous—that is, exposure has either occurred (yes) or not occurred (no)—breakdown into four groups is possible. There are a cases who were exposed and c cases who were not exposed. Similarly,

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TABLE 7.3 A Hypothetical Example of a Case-Control Study of Human Papillomavirus (HPV) and Cervical Cancer

	Cervical Cancer Cases	Controls
HPV positive	112	176
HPV negative	88	224
Totals	200	400
% HPV positive	56	44

there are b controls who were exposed and d controls who were not exposed. Thus the total number of cases is $(a + c)$ and the total number of controls is $(b + d)$. If exposure is associated with disease, we would expect the proportion of the cases who were exposed, $\left(\frac{a}{a+c}\right)$ to be greater than the proportion of the controls who were not exposed, $\left(\frac{b}{b+d}\right)$.

A hypothetical example of a case-control study is seen in Table 7.3. We are conducting a case-control study of whether human papillomavirus (HPV) is related to cervical cancer. We start with 200 people with cervical cancer (cases) and compare them to 400 people without cervical cancer (controls). If there is a relationship between HPV and cervical cancer, we would anticipate that a greater proportion of the cervical cancer cases than of the controls have HPV (i.e., have been exposed). Let's say we find that of the 200 cervical cancer cases, 112 were HPV-positive and 88 were HPV-negative. Of the 400 controls, 176 were HPV-positive and 224 were HPV-negative. Thus 56% of cervical cancer cases were HPV-positive compared to 44% of the controls. This calculation is only a first step. Further calculations to determine if there is an association of the exposure with the disease will be discussed later. This chapter focuses exclusively on issues of design in case-control studies.

Parenthetically, it is of interest to note that if we use only the data from a case-control study, we cannot estimate the prevalence of the disease. In this example we had 200 cases and 400 controls, but this does not imply that the prevalence is 33%, or $\left(\frac{200}{200+400}\right)$. The decision as to the number of controls to select per case in a case-control study is in the hands of the investigator and does not reflect the prevalence of disease in the population. In this example, the investigator could have selected 200 cases and 200 controls (1 control per case), or 200 cases and 800 controls (4 controls per case). Because the proportion of the entire study population that consists of cases is determined by the ratio of controls per case, and this proportion is determined by the investigator, it clearly does not reflect the true prevalence of the disease in the population in which the study is carried out.

At this point, we should emphasize that the hallmark of the case-control study is that it begins with people with the disease (cases) and compares them to people without the disease (controls). In other words, we identify the study participants based on the presence or absence of the outcome (the disease) of interest. This is in contrast to the design of a cohort study that will be discussed in Chapter 8, which begins with a group of exposed people and compares them to an unexposed group, all of whom are free of the disease at baseline or at the time of enrollment to the study. Some people have the erroneous impression that the distinction between the two types of study design is that cohort studies go forward in time and case-control studies go backward in time. Such a distinction is not correct; in fact, it is unfortunate that the term *retrospective* has been used for case-control studies, because the term incorrectly implies that calendar time is the characteristic that distinguishes case-control from cohort design. As will be shown in Chapter 8, a retrospective cohort study also uses data obtained in the past. Thus, calendar time is not the characteristic that distinguishes a case-control from a cohort study. What distinguishes the two study designs is whether the study begins with diseased and non-diseased people (case-control study) or with exposed and unexposed people (cohort study). One of the earliest studies of cigarette smoking and lung cancer was conducted by Sir Richard Doll (1912–2005) and Sir Austin Bradford Hill (1897–1991). Doll was an internationally known epidemiologist, and Hill was a well-known statistician and epidemiologist; together they developed the "Bradford Hill" guidelines for evaluating whether an observed association is causal.[15] Both men were knighted in the United Kingdom for their scientific work in epidemiology and biostatistics.

TABLE 7.4 Distribution of 1,357 Male Lung Cancer Patients and a Male Control Group According to Average Number of Cigarettes Smoked Daily Over the 10 Years Preceding Onset of the Current Illness

Average Daily Cigarettes	Lung Cancer Patients	Control Group
0	7	61
1–4	55	129
5–14	489	570
15–24	475	431
25–49	293	154
50+	38	12
Total	1,357	1,357

From Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. *BMJ*. 1952;2:1271-1286.

Table 7.4 presents data from their frequently cited study of 1,357 males with lung cancer and 1,357 controls according to the average number of cigarettes smoked per day in the 10 years preceding the present illness.[15] We see that there are fewer heavy smokers among the controls and very few nonsmokers among the lung cancer cases, a finding strongly suggestive of an association between smoking and lung cancer. In contrast to the previous example, exposure in this study is not just dichotomized (exposed or not exposed), but the exposure data are further stratified in terms of dose, as measured by the usual number of cigarettes smoked per day. Because many of the environmental exposures about which we are concerned today are not all-or-nothing exposures, the possibility of doing a study and analysis that takes into account the dose of the exposure is very important.

Other early case-control studies include those from Morton Levin and collaborators and from Wynder and Graham.[16,17] These studies preceded the Doll-Hill publication cited earlier. The study by Levin et al. had a number of strengths. History of tobacco use was obtained routinely before the final diagnosis was established, thus avoiding recall bias (see the next section); in addition, they found that the proportion of smokers in cases was greater than that in three types of controls (non-cases): cancers other than lung cancer, lung non-tumors, and other noncancer diagnoses.

Potential Biases in Case-Control Studies

Selection Bias

Sources of cases. In a case-control study, cases can be selected from a variety of sources, including hospital patients, patients in physicians' practices, or clinic patients. Many communities maintain registries of patients with certain diseases, such as cancer and end-stage renal disease, and such registries can serve as valuable sources of cases for such studies.

Several problems must be kept in mind when selecting cases for a case-control study. If cases are selected from a single hospital, any risk factors that are identified may be unique to that hospital due to referral patterns or other factors, and the results may not be generalizable to all patients with the disease. Consequently, if hospitalized cases are to be used, it is desirable to select the cases from several hospitals in the community. Furthermore, if the hospital from which the cases are drawn is a tertiary care facility, which selectively admits a large number of severely ill patients, any risk factors identified in the study may be risk factors only in persons with severe forms of the disease. In any event, it is essential that in case-control studies, just as in randomized trials, the criteria for eligibility be carefully specified in writing before the study is begun.

Using incident or prevalent cases. An important consideration in case-control studies is whether to include incident cases of a disease (newly diagnosed cases) or prevalent cases of the disease (people who may have had the disease for some time). The problem with the use of incident cases is that we must often wait for new cases to be diagnosed; whereas if we use prevalent cases, which have already been diagnosed, a larger number of cases is often available for study. However, despite this practical advantage of using prevalent cases, it is generally preferable to use incident cases of the disease in case-control studies of disease etiology. The reason is that any risk factors we may identify in a study using prevalent cases may be related more to *survival* with the disease than to the development of the disease *(incidence),* which introduces selection bias. If, for example, most people who develop the disease die soon after diagnosis, they will be underrepresented in a study that uses prevalent cases, and such a study is more likely to

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include longer-term survivors. This would constitute a highly nonrepresentative group of cases, and any risk factors identified with this nonrepresentative group may not be a general characteristic of all patients with the disease, but only of survivors.

Even if we include only *incident* cases (patients who have been newly diagnosed with the disease) in a case-control study, we will of course be excluding any patients who may have died before the diagnosis was made. There is no easy solution to this problem or to certain other problems in case selection, but it is important that we keep these issues in mind when we finally interpret the data and derive conclusions from the study. At that time, it is critical to consider possible selection biases that may have been introduced by the study design and by the manner in which the study was conducted.

Selection of Controls

In 1929, Raymond Pearl, professor of biostatistics at Johns Hopkins University in Baltimore, Maryland, conducted a study to test the hypothesis that tuberculosis protected against cancer.[18] From 7500 consecutive autopsies at Johns Hopkins Hospital, Pearl identified 816 cases of cancer. He then selected a control group of 816 from among the others on whom autopsies had been carried out at Johns Hopkins and determined the percentages of the cases and of the controls who had findings of tuberculosis on autopsy. Pearl's findings are seen in Table 7.5.

Of the 816 autopsies of patients with cancer, 54 had tuberculosis (6.6%), whereas of the 816 controls with no cancer, 133 had tuberculosis (16.3%). From the finding that the prevalence of tuberculosis was considerably higher in the control group (no cancer findings) than in the case group (cancer diagnoses), Pearl concluded that tuberculosis had an antagonistic or protective effect against cancer.

TABLE 7.5 Summary of Data from Pearl's Study of Cancer and Tuberculosis

	Cases (With Cancer)	Controls (Without Cancer)
Total no. of autopsies	816	816
No. (%) of autopsies with tuberculosis	54 (6.6)	133 (16.3)

From Pearl R. Cancer and tuberculosis. *Am J Hyg.* 1929;9: 97-159.

Was Pearl's conclusion justified? The answer to this question depends on the adequacy of his control group. If the prevalence of tuberculosis in the *noncancer* patients was similar to all people who were free of cancer, his conclusion would be valid. But that was not the case. At the time of the study, tuberculosis was one of the major reasons for hospitalization at Johns Hopkins Hospital. Consequently, what Pearl had inadvertently done in choosing the cancer-free control group was to select a group in which many of the patients had been diagnosed with and hospitalized for tuberculosis. Pearl thought that the control group's rate of tuberculosis would represent the level of tuberculosis expected in the general population, but because of the way he selected the controls, they came from a pool that was heavily weighted with tuberculosis patients, which did not represent the general population. He was, in effect, comparing the prevalence of tuberculosis in a group of patients with cancer with the prevalence of tuberculosis in a group of patients in which many had already been diagnosed with tuberculosis. Clearly his conclusion was not justified on the basis of these data.

How could Pearl have overcome this problem in his study? Instead of comparing his cancer patients with a group selected from all other autopsied patients, he *could have* compared the patients with cancer to a group of patients admitted for some specific diagnosis other than cancer (and not tuberculosis). In fact, Carlson and Bell[19] repeated Pearl's study but compared the patients who died of cancer with patients who died of heart disease at Johns Hopkins Hospital. They found no difference in the prevalence of tuberculosis at autopsy between the two groups. (It is of interest, however, that despite the methodologic limitations of Pearl's study, BCG, a vaccine against tuberculosis, is used today as a form of immunotherapy in several types of cancer.)

The problem with Pearl's study exemplifies the challenge of selecting appropriate controls as the fundamental component in drawing epidemiologically sound conclusions from case-control studies. Yet it remains one of the most difficult problems we confront in the conduct of epidemiologic studies using the case-control approach. The challenge is this: if we conduct a case-control study and find more exposure in the cases than

in the controls, we would like to be able to conclude that there is an association between the exposure and the disease in question. The way the controls are selected is a major determinant of whether such a conclusion is valid.

A fundamental conceptual issue relating to selection of controls is whether the controls should be similar to the cases in all respects other than having the disease in question, or whether they should be representative of all persons without the disease in the population from which the cases are selected. This question has stimulated considerable discussion, but in actuality the characteristics of the nondiseased people in the population from which the cases are selected are often not known, because the reference population may not be well defined.

Consider, for example, a case-control study using hospitalized cases. We want to identify the reference population that is the source of the cases so that we can then sample this reference population to select controls. Unfortunately, it is usually either not easy or not possible to identify such a reference population for hospitalized patients. Patients admitted to a hospital may come from the surrounding neighborhood, may live farther away in the same city, or may, through a referral process, come from another city or another country. Under these circumstances it is virtually impossible to define a specific reference population from which the cases emerged and from which we might select controls. Nevertheless, we want to design our study so that when it is completed, we can be reasonably certain that if we find a difference in exposure history between cases and controls, there are not likely to be any other important differences between them that might limit the inferences we may derive.

Sources of controls. Controls may be selected from nonhospitalized persons living in the community, from outpatient clinics in the same facilities where the cases were identified, or from hospitalized patients admitted for diseases other than that for which the cases were admitted. Which one of these is most appropriate? It depends on the research question and the objective of the study.

Use of nonhospitalized people as controls. Nonhospitalized controls may be selected from several sources in the community. Ideally, a probability sample of the reference population also known as the "study base" (the source of cases) might be selected, but as a practical matter, this is rarely possible. Other sources include school rosters, registered voters lists, and insurance company lists. Another option is to select, as a control for each case, a resident of a defined area, such as the neighborhood in which the case lives. Such *neighborhood controls* have been used for many years. In this approach, interviewers are instructed to identify the home of a case as a starting point, and from there walk past a specified number of houses in a specified direction and seek the first household that contains an eligible control. Because of increasing problems of security in urban areas of the United States, however, many people will no longer open their doors to interviewers. Nevertheless, in many other settings, the door-to-door approach to obtaining controls may be successful.

Because of the difficulties in many cities in the United States in obtaining neighborhood controls using the door-to-door approach, an alternative for selecting such controls has been to use telephone survey methods. Among these is random-digit dialing. Because telephone exchanges generally match neighborhood boundaries (being in the same area code), a case's seven-digit telephone number, of which the first three digits are the exchange, can be used to select a control telephone number, in which the terminal four digits of the phone number are randomly selected and the same three-digit exchange is used. In many low-income countries this approach is impractical, as only government offices and business establishments may have telephones. With the nearly universal mobile telephone coverage that now exists almost worldwide, the telephone is an intriguing method of control selection. Nevertheless, many persons screen their calls, and response rates are woefully low in our experience.

Another approach to control selection is to use a *best friend control.* In this approach, a person who has been selected as a case is asked for the name of a best friend who may be more likely to participate in the study knowing that his or her best friend is also participating. However, there are also disadvantages to this method of selecting controls. A best friend control obtained in this fashion may be similar to the case in age and in many other demographic and social characteristics. A resulting problem may be that the controls are too similar to the cases in regard to many variables, including the variables that are being investigated in the study. Sometimes, however, it may be useful to select a spouse or

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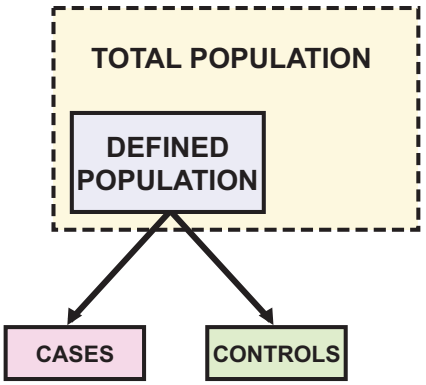

Fig. 7.9 Since both the cases and the hospital controls are selected from the defined population, any factors that affected admission of cases to a certain hospital would also affect the admission of hospital controls.

sibling control; a sibling may provide some control over genetic differences between cases and controls.

Use of hospitalized patients as controls. Hospital inpatients are often selected as controls because of the extent to which they are a "captive population," easily accessible and clearly identified; it should be relatively more economical to carry out a study using such controls. However, as just discussed, they represent a sample of an ill-defined reference population that usually cannot be characterized and thus to which results cannot be generalized. Moreover, hospital patients differ from people in the community. For example, the prevalence of cigarette smoking is known to be higher in hospitalized patients than in community residents; many of the diagnoses for which people are admitted to the hospital are smoking related.

Given that we generally cannot characterize the reference population from which hospitalized cases come, there is a conceptual attractiveness to comparing hospitalized cases with hospitalized controls from the same institution, who presumably would tend to come from the same reference population[a] (Fig. 7.9). Whatever selection factors in the referral system affected the cases' admission to a particular hospital would also pertain to the controls. However, referral patterns at the same hospital may differ for various clinical services; such an assumption may be questionable and generally it is often impossible to know whether it has been met.

When the decision has been made to use hospital controls, the question arises whether to use a sample of *all* other patients admitted to the hospital (other than those with the cases' diagnosis) or whether to select a *specific* "other diagnoses." If we wish to choose specific diagnostic groups, on what basis do we select those groups, and on what basis do we exclude others? The problem is that although it is attractive to select as hospitalized controls a disease group that is obviously unrelated to the putative causative factor under investigation, such controls are unlikely to be representative of the general reference population of non-cases. Taken to its logical end, it will not be clear whether it is the cases or the controls who differ from the general population.

The issue of which diagnostic groups would be eligible for use as controls and which would be ineligible (and therefore excluded) is very important. Let's say we are conducting a case-control study of smoking (exposure) and lung cancer (outcome): we select as cases patients who have been hospitalized with lung cancer, and as controls we select patients who have been hospitalized with emphysema. What problem would this present? Because we know that there is a strong relationship between smoking and emphysema, our controls, the emphysema patients, would include a high number of smokers. Consequently, any relationship of smoking to lung cancer would not be easy to detect in this study, because we would have selected as controls a group of persons in whom there is a much greater-than-expected prevalence of smoking (the exposure) than exists in the population. We might therefore want to exclude from our control group those persons who have other smoking-related diagnoses, such as CHD, bladder cancer, pancreatic cancer, and emphysema. Such exclusions might yield a control group with a lower-than-expected prevalence of smoking, and the exclusion process becomes overly complex. One alternative is to not exclude any groups from selection as controls in the design of the study, but to analyze the study data separately for different diagnostic subgroups that constitute the control group. This, of course, will drive up the numbers of controls necessary and the expense and logistical difficulties that accompany an expanded sample size.

Problems in control selection. In a classic study published in 1981, the renowned epidemiologist Brian MacMahon and coworkers[20] reported a case-control

[a]In current jargon, the reference population is also known as the "study base."

TABLE 7.6 Distribution of Cases and Controls by Coffee-Drinking Habits and Estimates of Risk Ratios

		COFFEE DRINKING (CUPS/DAY)				
Sex	**Category**	**0**	**1–2**	**3–4**	**≥5**	**Total**
M	No. of cases	9	94	53	60	216
	No. of controls	32	119	74	82	307
	Adjusted relative risk[a]	1.0	2.6	2.3	2.6	2.6
	95% Confidence interval	—	1.2–5.5	1.0–5.3	1.2–5.8	1.2–5.4
F	No. of cases	11	59	53	28	151
	No. of controls	56	152	80	48	336
	Adjusted relative risk[a]	1.0	1.6	3.3	3.1	2.3
	95% Confidence interval	—	0.8–3.4	1.6–7.0	1.4–7.0	1.2–4.6

[a]Chi-square (Mantel extension) with equally spaced scores, adjusted over age in decades: 1.5 for men, 13.7 for women. Mantel-Haenszel estimates of risk ratios, adjusted over categories of age in decades. In all comparisons, the referent category was subjects who never drank coffee.

From MacMahon B, Yen S, Trichopoulos D, et al. Coffee and cancer of the pancreas. *N Engl J Med.* 1981;304:630-633.

study of cancer of the pancreas. The cases were patients with a histologically confirmed diagnosis of pancreatic cancer in 11 Boston and Rhode Island hospitals from 1974 to 1979. Controls were selected from patients who were hospitalized at the same time as the cases; they were selected from other inpatients hospitalized by the attending physicians who had hospitalized the cases. Excluded were non-White patients; those older than 79 years; patients with pancreatic, hepatobiliary tract, and smoking-related or alcohol-related diseases; and patients with cardiovascular disease, diabetes, respiratory or bladder cancer, and peptic ulcer. However, the authors did not exclude patients with other kinds of gastrointestinal diseases, such as diaphragmatic hernia, reflux, gastritis, and esophagitis.

One finding in this study was an apparent dose-response relationship between coffee drinking and cancer of the pancreas, particularly in women (Table 7.6). When such a relationship is observed, it is difficult to know whether the disease is *caused* by the coffee drinking or by some factor closely related to the coffee drinking. Because smoking is a known risk factor for cancer of the pancreas, and because coffee drinking was closely related to cigarette smoking at that time (it was rare to find a smoker who did not drink coffee), did MacMahon and others observe an association of coffee drinking with pancreatic cancer because the coffee caused the pancreatic cancer, or because coffee drinking is related to cigarette smoking, and cigarette smoking is known to be a risk factor for cancer of the pancreas? Recognizing this problem, the authors analyzed the data after stratifying for smoking history. The relationship with coffee drinking held both for current smokers and for those who had never smoked (Table 7.7).

This report aroused great interest in both the scientific and lay communities, particularly among coffee manufacturers. Given the widespread exposure of human beings to coffee, if the reported relationship were true, it would have major public health implications.

Let's examine the design of this study. The cases were White patients with cancer of the pancreas at 11 Boston and Rhode Island hospitals. The controls are of particular interest: After some exclusions, they were patients with other diseases who were hospitalized by the same physicians who had admitted the pancreatic cancer cases. That is, when a case had been identified, the attending physician was asked if another of his or her patients who was hospitalized at the same time for another condition could be interviewed as a control. This unusual method of control selection had a practical advantage: one of the major obstacles in obtaining participation of hospital controls in case-control studies is that permission to contact the patient is usually requested of the attending physician. The physicians are often not motivated to have their patients serve as controls, because the patients do not have the disease that is the focus of the study. By asking physicians who had

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TABLE 7.7 Estimates of Relative Risk[a] of Cancer of the Pancreas Associated With Use of Coffee and Cigarettes

	COFFEE DRINKING (CUPS/DAY)			
Cigarette Smoking Status	**0**	**1–2**	**≥3**	**Total[b]**
Never smoked	1.0	2.1	3.1	1.0
Ex-smokers	1.3	4.0	3.0	1.3
Current smokers	1.2	2.2	4.6	1.2 (0.9–1.8)
Total[a]	1.0	1.8 (1.0–3.0)	2.7 (1.6–4.7)	

Values in parentheses are 95% confidence intervals of the adjusted estimates.
[a]The referent category is the group that uses neither cigarettes nor coffee. Estimates are adjusted for sex and age in decades.
[b]Values are adjusted for the other variables, in addition to age and sex, and are expressed in relation to the lowest category of each variable.
From MacMahon B, Yen S, Trichopoulos D, et al. Coffee and cancer of the pancreas. *N Engl J Med.* 1981;304:630-633.

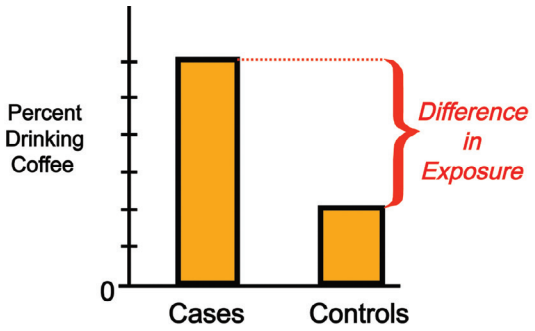

Fig. 7.10 Hypothetical example of a case-control study of coffee drinking and pancreatic cancer: cases have a higher level of coffee drinking than controls.

already given permission for patients with pancreatic cancer to participate, the likelihood was increased that permission would be granted for patients with other diseases to participate as controls.

Did that practical decision introduce any problems? The underlying question that the investigators wanted to answer was whether patients with cancer of the pancreas drank more coffee than people without cancer of the pancreas in the same population (Fig. 7.10). What MacMahon and coworkers found was that the level of coffee drinking in cases was greater than the level of coffee drinking in controls.

The investigators would like to be able to establish that the level of coffee drinking observed in the controls is what would be expected in the general population without pancreatic cancer and that cases therefore demonstrate *excessive* coffee drinking (Fig. 7.11A). But the problem is this: which physicians are most likely to admit patients with cancer of the pancreas to the hospital? Gastroenterologists are often the admitting physicians. Many of their other hospitalized patients (who served as controls) also have gastrointestinal problems, such as esophagitis and gastritis (as mentioned previously, patients with peptic ulcer were excluded from the control group). So, in this study, the persons who served as controls may very well have reduced their intake of coffee, either because of a physician's instructions or because of their own realization that reducing their coffee intake could relieve their symptoms. We cannot assume that the controls' levels of coffee drinking are representative of the level of coffee drinking expected in the general population—their rate of coffee drinking may be abnormally low. Thus, the observed difference in coffee drinking between pancreatic cancer cases and controls may not necessarily have been the result of cases drinking more coffee than expected, but rather of the controls drinking less coffee than expected (see Fig. 7.11B).

MacMahon and his colleagues subsequently repeated their analysis but separated controls with gastrointestinal illness from controls with other conditions. They found that the risk associated with coffee drinking was indeed higher when the comparison was with controls with gastrointestinal illness but that the relationship between coffee drinking and pancreatic cancer persisted, albeit at a lower level, even when the comparison was with controls with other illnesses. This became a classic example for what problematic selection of controls could

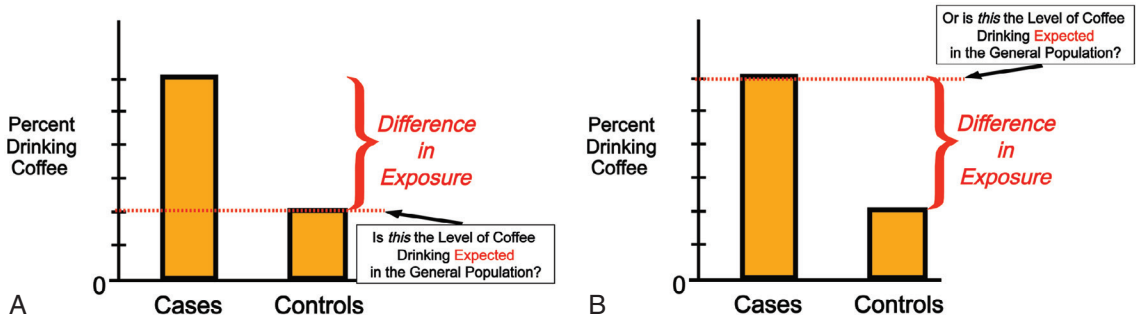

Fig. 7.11 Interpreting the results of a case-control study of coffee drinking and pancreatic cancer. **(A)** Is the lower level of coffee drinking in the controls the expected level of coffee drinking in the general population? *OR* **(B)** Is the higher level of coffee drinking in the cases the expected level of coffee drinking in the general population?

do to interpreting the results of a case-control study. Several years later, Hsieh and coworkers reported a new study that attempted to replicate these results; their findings did not support MacMahon's original findings.[21]

In summary, when a difference in exposure is observed between cases and controls, we must ask whether the level of exposure observed in the controls is really the level expected in the population in which the study was carried out or whether—perhaps given the manner of selection—the controls may have a particularly high or low level of exposure that might not be representative of the level in the population in which the study was carried out.

Information Bias

Problems of recall. An often-cited problem in case-control studies is that of recall of a history of past exposure. Recall problems are of two types: limitations in *recall* and *recall bias*. Recall bias is the main mechanism of information bias in case-control studies. The problem of recall is not limited to the case-control study design. Most epidemiologic studies inquire about life histories and are thus subject to recall biases. Survey research has identified many ways to mitigate the amount of bias associated with interviewing participants about events in their lives. However, many study participants forget about exposures or other events, tend to bring events that happened long ago forward in time ("telescoping"), and may be reticent to admit to practices that might be considered stigmatizing.

Limitations in Recall. Much of the information relating to exposure in case-control studies often involves collecting data from subjects by interviewer-administered questionnaires or by computerized assessment. Because virtually all human beings are limited to varying degrees in their ability to recall information, limitations in recall is an important issue in such studies. A related issue that is somewhat different from limitations in recall is that persons being interviewed may simply not have the information being requested.

This was demonstrated years ago in an historic study carried out by Abraham Lilienfeld and Saxon Graham published in 1958.[22] At that time, considerable interest centered on the observation that cancer of the cervix was highly unusual in two groups of women: Jewish women and Catholic nuns. This observation suggested that an important risk factor for cervical cancer could be sexual intercourse with an uncircumcised man, and several studies were carried out to confirm this hypothesis. However, the authors were skeptical about the validity of the responses regarding circumcision status. To address this question, they asked a group of men whether or not they had been circumcised. The men were then examined by a physician. As seen in Table 7.8, of the 56 men who stated they were circumcised, 19, or 33.9%, were found to be uncircumcised. Of the 136 men who stated they were not circumcised, 47, or 34.6%, were found to be circumcised. These data demonstrate that the findings from studies using interview data may not always be clear-cut.

Table 7.9 shows more recent data (2002)[23] regarding the relationship of self-reported circumcision to actual circumcision status. These data suggest that men have improved in their knowledge and reporting of their circumcision status, or the differences observed may be due to the studies having been conducted in different

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TABLE 7.8 Comparison of Patients' Statements With Examination Findings Concerning Circumcision Status, Roswell Park Memorial Institute, Buffalo, New York

Examination Finding	PATIENTS' STATEMENTS REGARDING CIRCUMCISION			
	Yes		No	
	No.	%	No.	%
Circumcised	37	66.1	47	34.6
Not circumcised	19	33.9	89	65.4
Total	56	100.0	136	100.0

Modified from Lilienfeld AM, Graham S. Validity of determining circumcision status by questionnaire as related to epidemiologic studies of cancer of the cervix. *J Natl Cancer Inst.* 1958;21:713-720.

TABLE 7.9 Comparison of Patients' Statements With Physicians' Examination Findings Concerning Circumcision Status in the Study of Circumcision, Penile Human Papillomavirus, and Cervical Cancer

Physician Examination Findings	PATIENTS' STATEMENTS REGARDING CIRCUMCISION			
	Yes		No	
	No.	%	No.	%
Circumcised	282	98.3	37	7.4
Not circumcised	5	1.7	466	92.6
Total	287	100.0	503	100.0

Modified from Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med.* 2002;346:1105-1112.

countries. There may also have been methodological differences, which could have accounted for the different results between the two studies.

If a limitation of recall regarding exposure affects all subjects in a study to the same extent, regardless of whether they are cases or controls, a misclassification of exposure status may result. Some of the cases or controls who were truly exposed will be erroneously classified as unexposed, and some who were actually not exposed will be erroneously classified as exposed. For exposures that have only two categories (e.g., "yes" vs. "no"), this leads to an underestimate of the true risk of the disease associated with the exposure (that is, there will be a tendency to bias the results toward a null finding, i.e., towards the exposure not being associated with the disease).

Recall Bias. A more serious potential problem in case-control studies is that of recall bias. Suppose that we are studying the possible relationship of congenital malformations to prenatal infections. We conduct a case-control study and interview mothers of children with congenital malformations (cases) and mothers of children without malformations (controls). Each mother is questioned about infections she may have had during the pregnancy.

A mother who has had a child with a birth defect often tries to identify some unusual event that occurred during her pregnancy with that child. She wants to know whether the abnormality was caused by something she did. Why did it happen? Such a mother may even recall an event, such as a mild respiratory infection, that a mother of a child without a birth defect may not even notice or may have forgotten entirely. This type of bias is known as *recall* bias; Ernst Wynder, a well-known epidemiologist, also called it "*rumination bias*."

In the study just mentioned, let's assume that the true infection rate during pregnancy in mothers of malformed infants and in mothers of normal infants is 15%—that is, there is no difference in infection rates. Suppose that mothers of malformed infants recall 60% of any infections they had during pregnancy, and mothers of normal infants recall only 10% of infections they had during pregnancy. As seen in Table 7.10, the *apparent* infection rate estimated from this case-control study using interviews would be 9% for mothers of malformed infants and 1.5% for mothers of control infants. Thus, the *differential recall* between cases and controls introduces a recall bias into the study that could artifactually suggest a relation of congenital malformations and prenatal infections. Although a potential for recall bias is self-evident in case-control studies, in point of fact, few actual examples demonstrate that recall bias has been a major problem in case-control studies and has led to erroneous conclusions regarding associations. The small number of examples available could reflect infrequent occurrence of such bias, or the fact that the data needed to clearly demonstrate the existence of such

TABLE 7.10 Example of an Artificial Association Resulting From Recall Bias: A Hypothetical Study of Maternal Infections During Pregnancy and Congenital Malformations

	Cases (With Congenital Malformations)	Controls (Without Congenital Malformations)
Assume That:		
True incidence of infection (%)	15	15
Infections recalled (%)	60	10
Result Will Be:		
Infection rate as ascertained by interview (%)	9.0	1.5

bias in a certain study are frequently not available. Nevertheless, the potential problem cannot be disregarded, and the possibility for such bias must always be kept in mind.

Other Issues in Case-Control Studies

Matching

A major concern in conducting a case-control study is that cases and controls may differ in characteristics or exposures other than the one that has been targeted for study. If more cases than controls are found to have been exposed, we may be left with the question of whether the observed association could be due to differences between the cases and controls in factors other than the exposure being studied. These factors are called *confounders*. For example, if more cases than controls are found to have been exposed, and if most of the cases are of low income and most of the controls are of high income, we would not know whether the factor determining development of disease is exposure to the factor being studied or another characteristic associated with having low income. To avoid such a situation, we would like to ensure that the distribution of the cases and controls by socioeconomic status is similar, so that a difference in exposure will likely constitute the critical difference, and the presence or absence of disease is not likely to be attributable to a difference in socioeconomic status. We will discuss confounding in detail in Chapter 15.

One approach to dealing with this problem in the design and conduct of the study is to match the cases and controls for factors about which we may be concerned, such as income, as in the preceding example. *Matching* is defined as the process of selecting the controls so that they are similar to the cases in certain characteristics, such as age, race, sex, socioeconomic status, and occupation. Matching may be of two types: (1) group matching and (2) individual matching. It is very important to distinguish between the two types, since each has its own implications for the statistical analysis of the case-control study, which is not discussed in this book.

Group matching. *Group matching* (or *frequency matching*) consists of selecting the controls in such a manner that the *proportion* of controls with a certain characteristic is *identical* to the proportion of cases with the same characteristic. Thus, if 25% of the cases are married, the controls will be selected so that 25% of that group is also married. This type of selection generally requires that all cases be selected first. After calculations are made of the proportions of certain characteristics in the group of cases, then a control group, in which the same characteristics occur in the same proportions, is selected. In general, when group matching, we never achieve *exactly* the same proportions of the key characteristic in cases and controls. When group matching is done for age, for example, the distribution that is the same in cases and controls is of the age groups (e.g., 45 to 49, 50 to 54); within each group, however, there may still be differences between cases and controls that must be considered: for example, although 10% of cases and controls are 50 to 54 years old, there may be a higher proportion of cases closer to age 54 than that of controls.

Individual matching. A second type of matching is *individual matching* (or *matched pairs*). In this approach, for each case selected for the study, a control is selected who is similar to the case in terms of the specific variable or variables of concern. For example, if the first case enrolled in our study is a 45-year-old White female, we will seek a 45-year-old White female control. If the second case is a 24-year-old Black man, we will select a control who is also a 24-year-old Black man. This type of control selection yields matched case-control pairs—that is, each case is individually matched

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to a control. In our hypothetical case, we would absolutely match the cases by gender and race/ethnicity, but we might use a 3- or 5-year bound for age. Thus, we might match a 45-year-old White woman with a 42- to 48-year-old White woman control. The implications of this method of control selection for the estimation of excess risk are discussed in Chapter 12.

Individual matching is often used in case-control studies that use hospital controls. The reason for this is more practical than conceptual. Let's say that sex determined at birth and age are considered important variables, and it is thought to be important that the cases and the controls be comparable in terms of these two characteristics. There is generally no practical way to dip into a pool of hospital patients to select a group with certain sex and age characteristics. Rather, it is easier to identify a case and then choose the next hospital admission that matches the case for sex and age. Thus, individual matching is most expedient in studies using hospital controls.

What are the problems with matching? The problems with matching are of two types: *practical* and *conceptual*.

Practical problems with matching. If an attempt is made to match according to too many characteristics, it may prove difficult or impossible to identify appropriate controls. For example, suppose that it is decided to match each case for race, sex, age, marital status, number of children, ZIP code of residence, and occupation. If the case is a 48-year-old Black woman who is married, has four children, lives in ZIP code 21209, and works in a photo-processing plant, it may prove difficult or impossible to find a control who is similar to the case in all of these characteristics. Therefore, the more variables on which we choose to match, the more difficult it will be to find a suitable control. Overmatching also leads to an inability to statistically analyze variables used in matching, as we address next.

Conceptual problems with matching. Perhaps a more important problem is the conceptual one: once we have matched controls to cases according to a given characteristic, we cannot study that characteristic. For example, suppose we are interested in studying marital status as a risk factor for breast cancer. If we match the cases (breast cancer) and the controls (no breast cancer) for marital status, we can no longer study if marital status is a risk factor for breast cancer. Why not? Because in matching according to marital status, we have artificially established an identical proportion in cases and controls: if 35% of the cases are married, and through matching we create a control group in which 35% are also married, we have artificially ensured that the proportion of married subjects will be identical in both groups. By using matching to impose comparability for a certain factor, we ensure the same prevalence of that factor in the cases and the controls. Clearly, we will not be able to ask whether cases differ from controls in the prevalence of that factor. We would therefore not want to match on the variable of marital status in this study; rather we want to determine if marital status is associated with the disease (breast cancer). Indeed, we do not want to match on *any* variable that we may wish to explore in our study.

It is also important to recognize that unplanned matching may inadvertently occur in case-control studies. For example, if we use neighborhood controls, we are in effect matching for socioeconomic status as well as for cultural and other characteristics of a neighborhood. If we use best-friend controls, it is likely that the case and their best friend share many lifestyle characteristics, which in effect produces a match for these characteristics. For example, in a study of oral contraceptive use and cervical cancer in which best-friend controls were considered, there was concern that if the case used oral contraceptives, it might well be that her best friend would also be likely to be an oral contraceptive user. The result would be an unplanned matching on oral contraceptive use, so that this variable could no longer be investigated in this study. This can be demonstrated in the case-control study of Celentano et al.[24] in which they explored the association between contraceptive use and cervical cancer in women through the Maryland Cervical Cancer Case-Control Study. The cases were identified through the Division of Gynecologic Oncology at The Johns Hopkins Hospital between 1982 and 1984 who had histologically confirmed invasive cervical cancer. The controls were identified from those who were residing in the same neighborhood (block in urban areas, neighborhood in suburbs, and post office in rural areas), and also through *case nomination* at the end of the in-home interview, in which the cases were asked to name several female neighbors, relatives, or friends who were about their same age and race who they thought had not had a hysterectomy. Another and less subtle example would be to match cases and controls on residence when doing a study of the relationship of air pollution to respiratory disease. Unplanned matching on a

variable that is strongly related to the exposure being investigated in the study is called *overmatching*. (Even in studies without overmatching, enforcing similarity between cases and controls on these variables through non-matched statistical approaches may also result in this kind of situation ["*overadjustment*"].)

In carrying out a case-control study, therefore, we match only on variables that we are convinced are risk factors for the disease, but which are not of primary interest in the study.

Use of Multiple Controls

Early in this chapter, we noted that the investigator can determine how many controls will be used per case in a case-control study and that multiple controls for each case are frequently used. Matching 2 : 1, 3 : 1 or 4 : 1 when selecting controls of the same type will increase the statistical power of our study Therefore many case-control studies will have more controls than cases. In addition to selecting *controls of the same type*, some studies select *controls of different types*, such as hospital and neighborhood controls or controls with different diseases.

Controls of the same type. Multiple controls of the *same type*, such as two controls or three controls for each case, are used to increase the statistical power of the study. Practically speaking, a noticeable increase in power is gained only up to a ratio of about 1 case to 4 controls. One might ask, "Why use multiple controls for each case? Why not keep the ratio of controls to cases at 1 : 1 and just increase the number of cases?" The answer is that for many of the relatively infrequent diseases we study (which are best studied using case-control designs), there may be a limit to the number of potential cases available for study. A clinic may see only a certain number of patients with a given cancer or with a certain connective tissue disorder each year. Because the number of cases cannot be increased without either extending the study in time to enroll more cases or developing a collaborative multicenter study, the option of increasing the number of controls per case is often chosen. These controls are of the same type (e.g., neighborhood controls)—only the ratio of controls to cases has changed.

Multiple controls of different types. In contrast, we may choose to use *multiple controls of different types*. For example, we may be concerned that the exposure of the hospital controls used in our study may not represent the rate of exposure that is "expected" in a population of nondiseased persons—that is, the controls may be a highly selected subset of nondiseased individuals and may have a different exposure experience. We mentioned earlier that hospitalized patients smoke more than people living in the community, and we are concerned because we do not know what the prevalence level of smoking in hospitalized controls represents or how to interpret a comparison of these rates with those of the cases. To address this problem, we may choose to use an additional control group, such as neighborhood controls. The hope is that the results obtained when cases are compared with hospital controls will be similar to the results obtained when cases are compared with neighborhood controls. If the findings differ, the reason for the discrepancy should be sought. In using multiple controls of different types, the investigator should ideally decide which comparison will be considered the "gold standard of truth" before embarking on the actual study.

In 1979, Ellen Gold and coworkers published a case-control study of brain tumors in children.[25] They used two types of controls: children with no cancer (called *normal controls*) and children with cancers other than brain tumors (called *cancer controls*; Fig. 7.12). What was the rationale for using these two control groups?

Let's consider the question, "Did mothers of children with brain tumors have more prenatal radiation exposure than control mothers?" Some possible results are seen in Fig. 7.13A.

If the radiation exposure of mothers of children with brain tumors is found to be greater than that of mothers of normal controls, and the radiation exposure of mothers of children with other cancers is also found to be greater than that of mothers of healthy children, what are the possible explanations? One conclusion might be that prenatal radiation is a risk factor both for brain

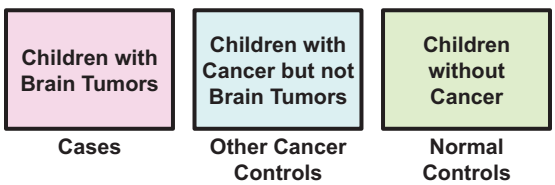

Fig. 7.12 Study groups of Gold et al. for brain tumors in children. (Data from Gold EB, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol*. 1979;109: 309-319.)

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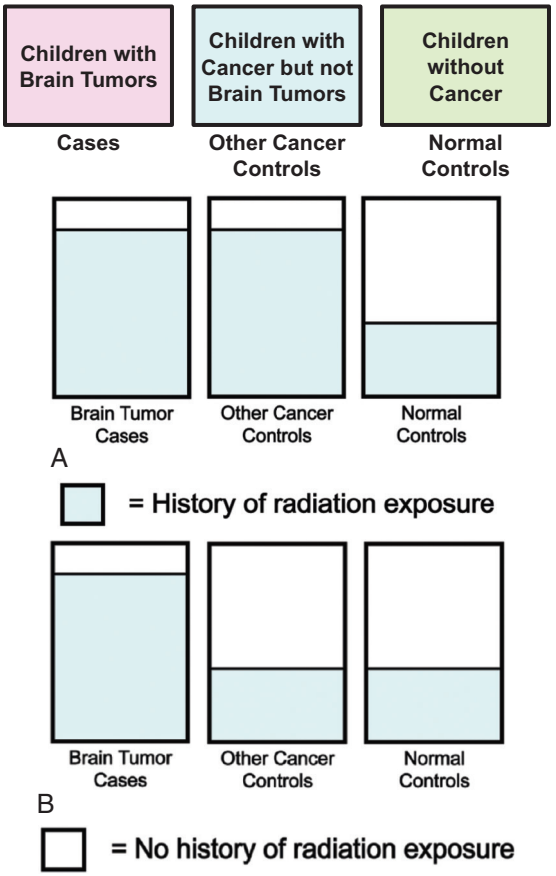

Fig. 7.13 Rationale for using two control groups: **(A)** Radiation exposure is the same in both brain tumor cases and in other cancer controls, but is higher in both groups than in normal controls: could this be due to recall bias? **(B)** Radiation exposure in other cancer controls is the same as in normal controls, but is lower than in brain tumor cases: recall bias is unlikely. (Data from Gold EB, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol.* 1979;109:309-319.)

tumors and for other cancers—that is, its effect is that of a carcinogen that is not site specific. Another explanation to consider is that the findings could have resulted from recall bias and that mothers of children with any type of cancer recall prenatal radiation exposure better than mothers of healthy children.

Consider another possible set of findings, shown in Fig. 7.13B. If mothers of children with brain tumors have a greater radiation exposure history than both mothers of normal controls and mothers of children with other cancers, the findings might suggest that prenatal radiation is a specific carcinogen for the brain. These findings would also reduce the likelihood that recall bias is playing a role, as it would seem implausible that mothers of children with brain tumors would recall prenatal radiation better than mothers of children with other cancers. Thus, multiple controls of different types can be valuable for exploring alternate hypotheses accounting for possible potential biases, such as recall bias.

Despite the issues raised in this chapter, case-control studies are invaluable in exploring the etiology of disease. Recent reports in the literature demonstrate the utility of the case-control study design in contemporary research.

Kristian Filion and colleagues in Canada addressed the concern that a common antidiabetic class of drugs (incretin-based drugs used in clinical practice) is associated with increased risk of heart failure.[26] Prior reports from clinical trials had been inconsistent. The investigators pooled health care data from four Canadian provinces, the United States, and the United Kingdom and conducted a case-control study in which each patient who was hospitalized for heart failure was matched with 20 controls. Matching criteria included age, sex, time entered into the study, how long diabetes had been treated, and how long patients with diabetes were under observation. Almost 30,000 patients were hospitalized for heart failure from almost 1.5 million total patients. Incretin-based medications were not found to increase hospitalization for heart failure when compared with oral antidiabetic drugs. Another example of the utility of the case-control study is given by Su and colleagues at the University of Michigan,[27] who evaluated the association of occupational and environmental exposures on the risk of developing amyotrophic lateral sclerosis (ALS, commonly known as *Lou Gehrig's disease*, a progressive neurological disease that affects the neurons in the brain and spinal cord responsible for controlling voluntary muscle movement).[27] Cases were identified at a tertiary referral center for ALS between 2011 and 2014. Cases consisted of 156 ALS patients; 128 controls were selected from volunteers who responded to online postings. Controls, who were frequency matched to cases by age, sex, and education, self-reported that they were free of neurodegenerative disease and had no first- or second-degree relatives with ALS. A questionnaire ascertained exposure to occupational and environmental exposures. Blood concentrations were assessed for 122 common pollutants. Overall, 101 cases and 110 controls had complete demographic and pollutant data. From the occupational history, military service was

associated with ALS. Self-reported pesticide exposure was associated with fivefold increased odds of ALS. When controlling for other possible factors that might be associated with ALS, three exposures measured in the blood were identified: occupational exposures to pesticides and to polychlorinated biphenyls (PCBs) in farming and fishing industries. The authors concluded that persistent environmental pollutants as measured in the blood were significantly associated with ALS and suggested that reducing exposure to these agents might reduce the incidence of ALS at the population level.

A final example of the usefulness of the case-control study relates to its use during a disease outbreak. A matched case-control study addressing the household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2) was published in late 2021.[28] The cases for this study were obtained from national surveillance data in England. The controls were cases where no further SARS-CoV-2 cases were reported in the household in the subsequent 14 days. Cases and controls were matched on a 1:2 ratio. The authors found that the odds ratio of household transmission was 1.70 among Delta variant cases (95% CI 1.48–1.95, $P < .001$) compared to Alpha cases after adjusting for potential confounders. This was an important study to understand the transmissibility of the COVID-19 Delta variant and how it replaced the Alpha variant as the dominant variant in England in 2021 in a very short period.

When Is a Case-Control Study Warranted?

A case-control study is useful as a first step when searching for a cause of an adverse health outcome, as seen in the examples at the beginning of this chapter and those just presented. At an early stage in our search for an etiology, we may suspect any one of several exposures, but we may not have evidence, and certainly no strong evidence, to suggest an association of any one of the suspect exposures with the disease in question. Using the case-control design, we compare people with the disease (cases) and people without the disease (controls; Fig. 7.14A). We can then explore the possible roles of a variety of exposures or characteristics in causing the disease (see Fig. 7.14B). If the exposure is associated with the disease, we would expect the proportion of cases who have been exposed to be greater than the proportion of controls who have been exposed (see Fig. 7.14C). When such an association is documented in a case-control study, the next step is often to carry out a cohort study to further elucidate the relationship.

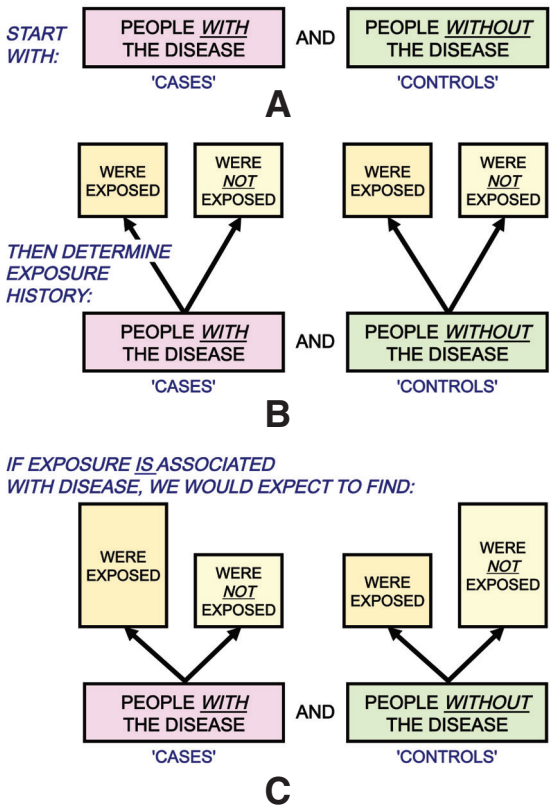

Fig. 7.14 Design of a case-control study. **(A)** Start with the cases and the controls. **(B)** Measure past exposure in both groups. **(C)** Expected findings if the exposure is associated with the disease.

Because case-control studies are generally less expensive than cohort studies and can be carried out more quickly, they are often the first step in determining whether an exposure is linked to an increased risk of disease.

Case-control studies are also valuable when the disease being investigated is rare. It is often possible to identify cases for study from disease registries, hospital records, or other sources. In contrast, if we conduct a cohort study for a rare disease, an extremely large study population may be needed in order to observe a sufficient number of individuals in the cohort develop the disease in question. In addition, depending on the length of the interval between exposure and development of disease, a cohort design may involve many years of follow-up of the cohort and considerable logistical difficulty and expense in maintaining and following the cohort over the study period.

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Case-Crossover Design

The *case-crossover design* is primarily used for studying the etiology of acute outcomes such as MIs or deaths from acute events in situations where the suspected exposure is transient, and its effect occurs over a short time. This type of design has been used in studying exposures such as air pollution characterized by rapid and transient increases in particulate matter. In this type of study, a case is identified (e.g., a person who has suffered an MI) and the level of the environmental exposure, such as level of airborne particulate matter, is ascertained for a short time period preceding the event (the at-risk period). This level is compared with the level of exposure in a control time period that is more remote from the event. Thus, each person who is a case serves as his own control, with the period immediately before his adverse outcome being compared with a "control" period at a prior time when no adverse outcome occurred. Importantly, in this type of study, there is inherent matching for variables that do not change (e.g., genetic factors) or variables that only change within a reasonably long period (e.g., height). The question being asked is "Was there any difference in exposure between the time period immediately preceding the outcome and a time period in the more remote past that was not immediately followed by any adverse health effect?"

Let's look at a very small hypothetical 4-month case-crossover study of air pollution and MI (Fig. 7.15A to E).

Fig. 7.15A shows that over a 4-month period, January–April, four cases of MI were identified, symbolized by the small red hearts in the diagrams. The vertical dotted lines delineate 1-month intervals during the 4-month period. For the same 4-month period, levels of air pollution were measured. Three periods of high levels of air pollution of different lengths of time were identified and are shown by the pink areas in Fig. 7.15B.

For each person with an MI in this study, an "at-risk" period (also called a "hazard period") was defined as the 2 weeks immediately prior to the event. These at-risk periods are indicated by the red brackets in Fig. 7.15C. If an exposure has a short-term effect on risk of an MI, we would expect exposure to have occurred during that 2-week at-risk period. The critical element, however, in a case-crossover design is that for each subject in the study, we compare the level of exposure in that at-risk period with a control period (also called a "referent period") that is unlikely to be relevant to occurrence of the event (the MI) because it is too far removed in time from the occurrence. In this example, the control period selected for each subject is a 2-week period beginning 1 month before the at-risk period, and these control periods are indicated by the blue brackets in Fig. 7.15D. Thus, as shown by the yellow arrows in Fig. 7.15E, for each subject, we are comparing the air pollution level in the at-risk period to the air pollution level in the control period. In order to demonstrate an association of MI with air pollution, we would expect to see greater exposure to high levels of air pollution during the at-risk period than during the control period.

In this example, we see that for subject 1 both the at-risk period and the control period were in low pollution times. For subjects 2 and 3, the at-risk periods were in high pollution times and the control periods in low pollution times. For subject 4, both the at-risk and control periods were in high pollution times.

Thus, in the case-crossover design, each subject serves as his or her own control. In this sense the case-crossover design is similar to the planned crossover design presented in Chapter 10. In this type of design, we are not concerned about other differences between the characteristics of the cases and those of a separate group of controls. This design also eliminates the additional cost that would be associated with identifying and interviewing a separate control population.

Attractive as this design is, unanswered questions remain. For example, the case-crossover design can be used to study people with heart attacks in regard to whether there was an episode of severe grief or anger during the period immediately preceding the attack. In this study design, the frequency of such emotionally charged events during that time interval would be compared, for example, with the frequency of such events during a period a month earlier, which was not associated with any adverse health event. Information on such events in both periods is often obtained by interviewing the subject. The question arises, however, whether there could be recall bias, in that a person may recall an emotionally charged episode that occurred shortly before a coronary event, while a comparable episode a month earlier in the absence of any adverse health event may remain forgotten. Thus, recall bias may be a problem not only when we compare cases and controls, as discussed earlier in this chapter, but also when we compare the same individual in two different time periods. Another problem with this design is that, although variables that do not change over time are intrinsically the same in the at-risk and the control periods, time-varying variables, however, such as weather or day of the week,

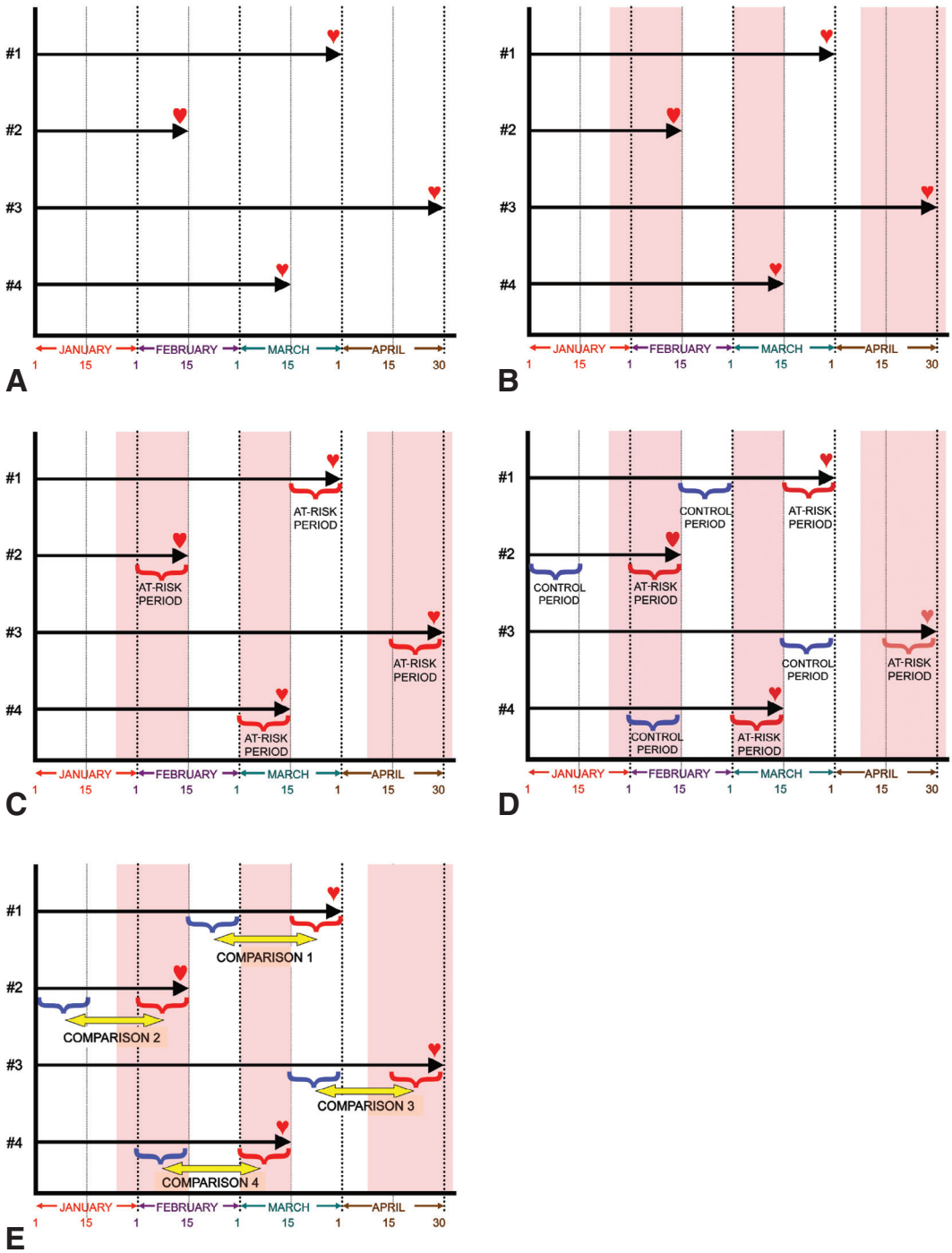

Fig. 7.15 Design and findings of a hypothetical 4-month case-crossover study of air pollution and myocardial infarction (MI; see discussion in text on page 176). **(A)** Times of development of MI cases. **(B)** Periods of high air pollution (shown by the *colored bands*). **(C)** Defining at-risk periods *(red brackets)*. **(D)** Defining control periods *(blue brackets)*. **(E)** Comparisons made of air pollution levels in at-risk and in control periods for each MI case in the study *(yellow arrows)*.

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TABLE 7.11 Finding Your Way in the Terminology Jungle

Case-control study		=		Retrospective study
Cohort study	=	Longitudinal study	=	Prospective study
Prospective cohort study	=	Concurrent cohort study	=	Concurrent prospective study
Retrospective cohort study	=	Historical cohort study	=	Nonconcurrent prospective study
Randomized trial		=		Experimental study
Cross-sectional study		=		Prevalence survey

may not be the same in these groups and, therefore, must be dealt with using special statistical techniques. Further discussion of case-crossover is provided by Maclure and Mittleman.[29]

CONCLUSION

We have now reviewed the most basic, yet very useful, observational designs used in epidemiologic investigations and clinical research. Unfortunately, a variety of different terms are used in the literature to describe different study designs, and it is important to be familiar with them. Table 7.11 is designed to help guide you through the often-confusing terminology. The next study design is the "cohort study," which is presented in Chapter 8, and builds upon what we have learned about the initial observational study designs presented in this chapter. We then follow with two chapters on randomized trials, which are not "strictly" observational studies. In observational studies, the investigator merely investigates those who are diseased or not diseased and determines whether they were exposed or not exposed to the risk factor under investigation. In the randomized trial study design, the investigator uses a random allocation schedule to determine which participants are exposed or not. Hence the randomized trial is akin to an experiment and is also known as an "experimental study." However, it differs from observational studies only in that the exposure is experimentally (randomly) assigned by the study investigator.

The purpose of all of these types of studies is to identify associations between exposures and diseases. If such associations are found, the next step is to determine whether the associations are likely to be causal. These topics, starting with estimating risk and determining whether exposure to a certain factor is associated with excess risk of the disease, are addressed subsequently.

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REVIEW QUESTIONS FOR CHAPTER 7

1. *A case-control study is characterized by all of the following* except:
- **a.** It is relatively inexpensive compared with most other epidemiologic study designs
- **b.** Patients with the disease (cases) are compared with persons without the disease (controls)
- **c.** Incidence rates may be computed directly
- **d.** Assessment of past exposure may be biased
- **e.** Definition of cases may be difficult

2. *Residents of three villages with three different types of water supply were asked to participate in a survey to identify cholera carriers. Because several cholera deaths had occurred recently, virtually everyone present at the time underwent examination. The proportion of residents in each village who were carriers was computed and compared. What is the proper classification for this study?*
- **a.** Cross-sectional study
- **b.** Case-control study
- **c.** Prospective cohort study
- **d.** Retrospective cohort study
- **e.** Experimental study

3. *Which of the following is a case-control study?*
- **a.** Study of past mortality or morbidity trends to permit estimates of the occurrence of disease in the future
- **b.** Analysis of previous research in different places and under different circumstances to permit the establishment of hypotheses based on cumulative knowledge of all known factors
- **c.** Obtaining histories and other information from a group of known cases and from a comparison group to determine the relative frequency of a characteristic or exposure under study
- **d.** Study of the incidence of cancer in men who have quit smoking
- **e.** Both *a* and *c*

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4. *In a study begun in 1965, a group of 3,000 adults in Baltimore were asked about alcohol consumption. The occurrence of cases of cancer between 1981 and 1995 was studied in this group. This is an example of:*
   - **a.** A cross-sectional study
   - **b.** A prospective cohort study
   - **c.** A retrospective cohort study
   - **d.** A clinical trial
   - **e.** A case-control study
5. *In a small pilot study, 12 women with endometrial cancer (cancer of the uterus) and 12 women with no apparent disease were contacted and asked whether they had ever used estrogen. Each woman with cancer was matched by age, race, weight, and parity to a woman without disease. What kind of study design is this?*
   - **a.** Prospective cohort study
   - **b.** Retrospective cohort study
   - **c.** Case-control study
   - **d.** Cross-sectional study
   - **e.** Experimental study
6. *The physical examination records of the entire incoming freshman class of 1935 at the University of Minnesota were examined in 1977 to see if their recorded height and weight at the time of admission to the university was related to the development of coronary heart disease (CHD) by 1986. This is an example of:*
   - **a.** A cross-sectional study
   - **b.** A case-control study
   - **c.** A prospective cohort study
   - **d.** A retrospective cohort study
   - **e.** An experimental study
7. *In a case-control study, which of the following is true?*
   - **a.** The proportion of cases with the exposure is compared with the proportion of controls with the exposure
   - **b.** Disease rates are compared for people with the factor of interest and for people without the factor of interest
   - **c.** The investigator may choose to have multiple comparison groups
   - **d.** Recall bias is a potential problem
   - **e.** *a, c,* and *d*
8. *In which one of the following types of study designs does a subject serve as their own control?*
   - **a.** Prospective cohort study
   - **b.** Retrospective cohort study
   - **c.** Case-cohort study
   - **d.** Case-crossover study
   - **e.** Case-control study
9. *Ecologic fallacy refers to:*
   - **a.** Assessing exposure in large groups rather than in many small groups
   - **b.** Assessing outcome in large groups rather than in many small groups
   - **c.** Ascribing the characteristics of a group to every individual in that group
   - **d.** Examining correlations of exposure and outcomes rather than time trends
   - **e.** Failure to examine temporal relationships between exposures and outcomes
10. *A researcher wants to investigate if tea consumption (assessed by a biomarker for tea metabolism) increases the risk of CHD. He uses a case-control study to answer this question. CHD is rare in younger people. Which two groups are best to enroll and compare for this purpose?*
    - **a.** The group of CHD cases and a group of those who do not have CHD individually matched to the cases for tea metabolism biomarker
    - **b.** The group of CHD cases and a group of those who do not have CHD frequency matched to the cases for tea metabolism biomarker
    - **c.** The group of CHD cases and a group of those who do not develop CHD, matched for age
    - **d.** A random sample of those who drink tea and a random sample of those who do not drink tea, matched for age
    - **e.** A random sample of those who drink tea and a random sample of those who do not drink tea, unmatched for age
11. *Which of the following is a true conclusion concerning matching?*
    - **a.** Once we have matched controls to cases according to a given characteristic, we can only study that characteristic when the prevalence of disease is low
    - **b.** If an attempt is made to match on too many characteristics, it may prove difficult or impossible to adjust for all of the characteristics during data analysis
    - **c.** Matching on many variables may make it difficult to find an appropriate control
    - **d.** Individual matching differs from frequency matching because controls are selected from hospitals instead of from the general population
    - **e.** None of the above

8

Cohort Studies

LEARNING OBJECTIVES

- To describe the designs of cohort studies and options for the conduct of longitudinal studies.
- To illustrate the cohort study design with two important historical examples.
- To discuss some potential biases in cohort studies.

In this chapter, and in the following chapters in Section II, we turn to the uses of epidemiology to elucidate etiologic or causal relationships. The two steps that underlie the study designs are discussed in this chapter and the chapters on clinical trials. Fig. 8.1 schematically represents these two conceptual steps:

1. First, we determine whether there is an *association* between a factor or a characteristic and the development of a disease. This can be accomplished by studying the characteristics of groups, by studying the characteristics of individuals, or both.
2. Second, we derive appropriate inferences regarding a possible *causal* relationship from the patterns of association that have been found.

Previously, we described the study designs used for step 1. In this chapter, cohort studies are discussed; randomized controlled trials (experiments) are presented in Chapters 10 and 11. Cohort studies, along with ecologic, cross-sectional, and case-control studies, in contrast to randomized controlled trials, are collectively referred to as *observational* studies. That is, there is no experimental manipulation involved; the investigator merely *observes* exposures and the disease in the study population. In other words, we investigate exposures among study participants (at one point in time or over time) and observe their outcomes either at the same point in time or sometime later on.

DESIGN OF A COHORT STUDY

In a cohort study, the investigator selects a group of exposed individuals and a group of unexposed individuals and follows both groups over time to compare the incidence of disease (or rate of death from disease) in the two groups (Fig. 8.2). The design may include more than two groups (such as no exposure, low exposure, and high exposure levels), although only two groups are shown here for diagrammatic purposes.

If a positive association exists between the exposure and the disease, we would expect that the proportion of the exposed group in whom the disease develops (incidence in the exposed group) would be greater than the proportion of the unexposed group in whom the disease develops (incidence in the unexposed group).

The calculations involved are seen in Table 8.1. We begin with an exposed group and an unexposed group. Of the $(a + b)$ exposed persons, the disease develops in a but not in b. Thus, the incidence of the disease among the exposed is $\frac{a}{a+b}$. Similarly, in the $(c + d)$ unexposed persons in the study, the disease develops in c but not in d. Thus, the incidence of the disease among the unexposed is $\frac{c}{c+d}$.

The use of these calculations is seen in a hypothetical example of a cohort study shown in Table 8.2. In this cohort study, the association of smoking with coronary heart disease (CHD) is investigated by selecting for study a group of 3,000 smokers (exposed) and a group of 5,000 nonsmokers (unexposed), all of whom are free of heart disease at baseline. Both groups are followed for the development of CHD, and the *incidence* of CHD in

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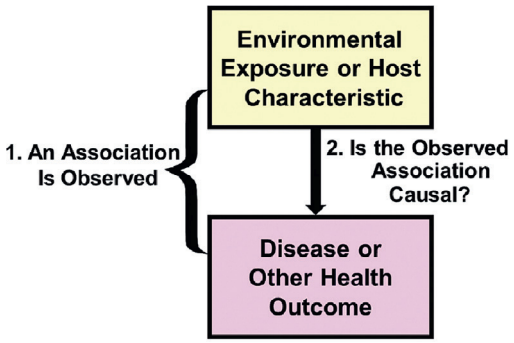

Fig. 8.1 If we observe an association between an exposure and a disease or another outcome *(1)*, the question is: Is the association causal *(2)*?

TABLE 8.1 Design of a Cohort Study

First Select	Exposed	a	b	$a+b$	$\frac{a}{a+b}$
	Not exposed	c	d	$c+d$	$\frac{c}{c+d}$

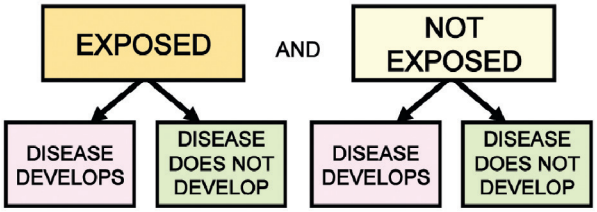

Fig. 8.2 Design of a cohort study.

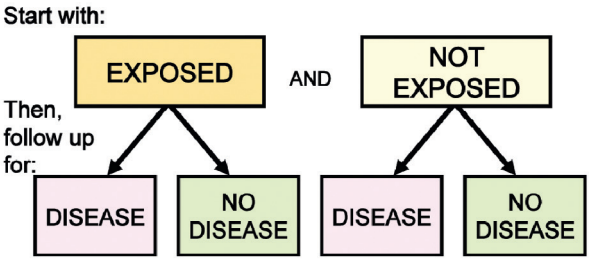

Fig. 8.3 Design of a cohort study beginning with exposed and unexposed groups.

TABLE 8.2 Results of a Hypothetical Cohort Study of Smoking and Coronary Heart Disease (CHD)

		THEN FOLLOW TO SEE WHETHER			
		CHD Develops	CHD Does Not Develop	Totals	Incidence per 1,000 per Year
First Select	Smoke cigarettes	84	2,916	3,000	28.0
	Do not smoke cigarettes	87	4,913	5,000	17.4

both groups is compared. CHD develops in 84 of the smokers and in 87 of the nonsmokers. The result is an incidence of CHD of 28.0/1,000 in the smokers and 17.4/1,000 in the nonsmokers.

Note that because we are identifying *new* (incident) cases of disease as they occur, we can determine whether a temporal relationship exists between the exposure and the disease (i.e., whether the exposure preceded the onset of the disease). Clearly, such a temporal relationship must be established if we are to consider the exposure a possible cause of the disease in question. Note that sometimes we may be interested in identifying *recurrent* cases. For example, we may be interested in determining the risk factors that are associated with experiencing a recurrent stroke among patients who had a previous stroke. The decision to examine *new* vs. *recurrent* cases depends on the specific research question being asked.

SELECTION OF STUDY POPULATIONS

The essential characteristic in the design of cohort studies is the comparison of outcomes in an exposed group and in an unexposed group (or a group with a certain characteristic and a group without that characteristic, such as older or younger participants, men and women). There are two basic ways to generate such groups:

1. We can create a study population by selecting groups for inclusion in the study by whether or not they were exposed (e.g., occupationally exposed cohorts compared with similarly aged community residents who do not work in those occupations) (Fig. 8.3).

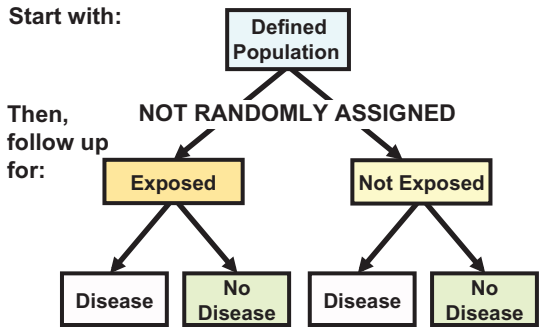

Fig. 8.4 Design of a cohort study beginning with a defined population.

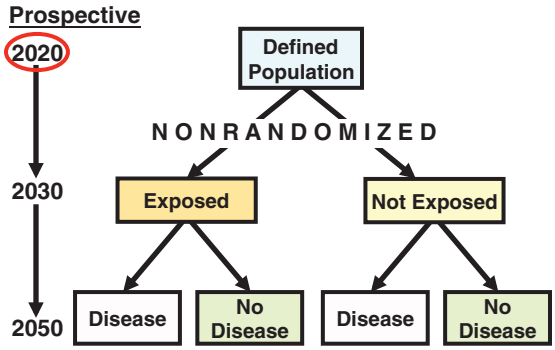

Fig. 8.5 Time frame for a hypothetical *concurrent* cohort study begun in 2020.

2. We can select a defined population before any of its members become exposed or before their exposures are identified. We could select a population on the basis of some factor not related to exposure (such as community of residence) (Fig. 8.4) and take histories of, or perform blood tests or other assays on, the entire population. Using the results of the histories or the tests, one can separate the population into *exposed* and *unexposed* groups (or those who have and those who do not have certain biologic characteristics), such as was done in the Framingham Study, described later in this chapter.

Cohort studies, in which we wait for an outcome to develop in a population, often require a long follow-up period, lasting until enough events (outcomes) have occurred. When the second approach is used—in which a population is identified for study based on some characteristic unrelated to the exposure in question—the exposure of interest may not take place for some time, even for many years after the population has been defined. Consequently, the length of follow-up required is even greater with the second approach than it is with the first. Note that with either approach the cohort study design is fundamentally the same: *we compare exposed and unexposed persons.* This comparison is the hallmark of the cohort design.

TYPES OF COHORT STUDIES

A major issue with the cohort design just described is that the study population often must be followed up for a long period to determine whether the outcome of interest develops. Consider as an example a hypothetical study of the relationship of smoking to lung cancer. We identify a population of elementary school students and follow them; 10 years later, when they are teenagers, we identify those who smoke and those who do not. We then follow both groups—smokers and nonsmokers—to see who develops lung cancer and who does not. Let us say that we begin our study in 2020 (Fig. 8.5). Let us suppose that many children who will become smokers will do so within 10 years. Exposure status (smoker or nonsmoker) will therefore be ascertained 10 years later, in the year 2030. For purposes of this example, let us assume that the average latent period from beginning smoking to development of lung disease is 20 years. Therefore, development of lung cancer will be, on average, ascertained 20 years later, in 2050.

This type of study design is called a *prospective cohort study* (also called by some a *concurrent cohort* or *longitudinal cohort study*[a]). It is *concurrent* (happening or done at the same time) because the investigator identifies the original population at the beginning of the study and, in effect, follows the subjects concurrently through calendar time until the point at which the disease develops or does not develop.

What is the problem with this approach? The difficulty is that, as just described, the study will take at least 30 years to complete. Several problems can result. If one is fortunate enough to obtain a research grant, such funding may be limited to a maximum of only 5 years. In addition, with a study of this length, there is the risk that the study subjects will outlive the investigator, or at least that the investigator may not survive to the end of the study. Given these issues, the concurrent cohort

[a]The term "longitudinal study" encompasses any study in which there is a follow-up time. This includes prospective and retrospective cohort studies and randomized controlled trials.

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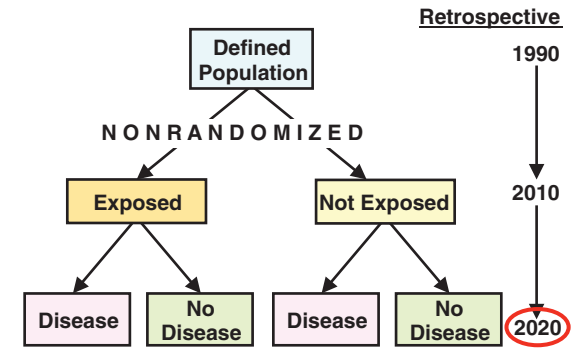

Fig. 8.6 Time frame for a hypothetical *nonconcurrent* cohort study begun in 2020.

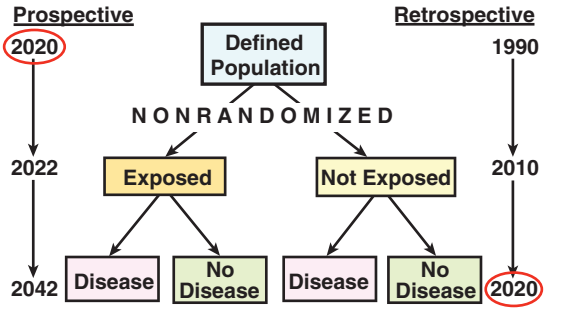

Fig. 8.7 Time frames for a hypothetical *concurrent* cohort study and a hypothetical *nonconcurrent* cohort study begun in 2012.

study often proves unattractive to investigators who are contemplating a new research question.

Do these problems mean that the cohort design is not practical? Is there any way to shorten the time needed to conduct a cohort study? Let us consider an alternate approach using the cohort design (Fig. 8.6). Suppose that we again begin our study in 2020, but now we find that an old roster of elementary schoolchildren from 1990 is available in our community and that they had been surveyed in high school regarding their smoking habits in 2010. Using these data resources in 2020, we can begin to determine who in this population developed lung cancer and who has not. This is called a *retrospective cohort* or *historical cohort study* (also called a *nonconcurrent study*). However, note that the study design does not differ from that of the *concurrent* cohort design—we are still comparing exposed and unexposed groups. What we have done in the *nonconcurrent* cohort design is to use historical data so that we can telescope (reduce) the frame of calendar time for the study and obtain our results sooner. It is no longer a *concurrent* design, because we are beginning the study with a preexisting population to reduce the duration of the study. However, as shown in Fig. 8.7, the *designs for both the concurrent cohort study and the nonconcurrent* or *historical cohort study are identical: we are comparing exposed and unexposed populations*. The only difference between them is calendar time. In a *concurrent cohort design*, exposure and nonexposure are ascertained as they occur during the study; the groups are then followed for several years into the future and incidence is measured. In a *nonconcurrent cohort design*, exposure is ascertained from past records and the outcome (development or no development of disease) is determined when the study is begun.

It is also possible to conduct a study that is a combination of *concurrent* cohort and *nonconcurrent* cohort designs. With this approach, exposure is ascertained from objective records in the past (as in a historical cohort study) and follow-up and measurement of outcome continue into the future.

EXAMPLES OF COHORT STUDIES

Example 1: The Framingham Study

One of the first, most important, and most widely known cohort studies is the Framingham Study of cardiovascular disease, which was begun in 1948.[1] Framingham is a town in Massachusetts, approximately 20 miles west of Boston. It was thought that the characteristics of its population (just less than 30,000 residents) would be appropriate for such a study and would facilitate follow-up of participants because migration out was considered to be low (i.e., the population was stable).

Residents were considered eligible if they were between 30 and 62 years of age at study initiation. The rationale for using this age range was that people younger than 30 years would generally be unlikely to manifest the cardiovascular end points being studied during the proposed 20-year follow-up period. Many persons older than 62 years would already have established coronary disease, and it would therefore not be rewarding to study persons in this age group for identifying the incidence of coronary disease.

The investigators sought a sample size of 5,000. Table 8.3 shows how the final study population was

TABLE 8.3 Derivation of the Framingham Study Population

	No. of Men	No. of Women	Total
Random sample	3,074	3,433	6,507
Respondents	2,024	2,445	4,469
Volunteers	312	428	740
Respondents free of CHD	1,975	2,418	4,393
Volunteers free of CHD	307	427	734
Total free of CHD: The Framingham Study Group	2,282	2,845	5,127

CHD, Coronary heart disease.
From Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann NY Acad Sci.* 1993;107:539–556.

derived. It consisted of 5,127 men and women who were between 30 and 62 years of age at the time of study entry and were free of cardiovascular disease at that time. In this study, many suggested "exposures" were defined, including age and sex, smoking, weight, blood pressure, cholesterol levels, physical activity, and other factors.

New coronary events (incidence) were identified by examining the study population every 2 years and by daily surveillance of hospitalizations at the only hospital in Framingham.

The study was designed to test the following hypotheses (that were untested at the time the study began but whose results we now take as "fact"):

- The incidence of CHD increases with age. It occurs earlier and more frequently in males.
- Persons with hypertension develop CHD at a greater rate than those who are normotensive.
- Elevated blood cholesterol level is associated with an increased risk of CHD.
- Tobacco smoking and habitual use of alcohol are associated with an increased incidence of CHD.
- Increased physical activity is associated with a decrease in the development of CHD.
- An increase in body weight predisposes a person to the development of CHD.
- An increased rate of development of CHD occurs in patients with diabetes mellitus.

When we examine this list nowadays, we might wonder why such obvious and well-known relationships should have been examined in such an extensive study. The danger of this "hindsight" approach should be kept in mind; it is primarily *because* of the Framingham Study, a classic cohort study that made fundamental contributions to our understanding of the epidemiology of cardiovascular disease, that these relationships are currently well known.

This study used the second method described earlier in the chapter for selecting a study population for a cohort study: A defined population was selected based on location of residence or other factors not related to the exposure(s) in question. The population was then observed over time to determine which individuals developed or already had the "exposure(s)" of interest and, later on, to determine which study participants developed the cardiovascular outcome(s) of interest.

This study design offered an important advantage: It permitted the investigators to study multiple "exposures," such as hypertension, smoking, obesity, cholesterol levels, and other factors, as well as the complex interactions among the exposures, by using multivariable techniques (studying multiple risks simultaneously). Thus, although a cohort study that begins with an exposed and an unexposed group focuses often on only one specific exposure, a cohort study that begins with a defined population can explore the roles of many exposures to the study outcome measure(s).

Example 2: Incidence of Breast Cancer and Progesterone Deficiency

It has long been recognized that breast cancer is more common in women who are older at the time of their first pregnancy. A difficult question is raised by this observation: Is the relationship between late age at first pregnancy and increased risk of breast cancer related to the finding that early first pregnancy protects against breast cancer (and therefore such protection is missing in women who have a later pregnancy or no pregnancy), or are both a delayed first pregnancy and an increased risk of breast cancer the result of some third factor, such as an underlying hormonal abnormality?

It is difficult to tease apart these two interpretations. However, in 1978, Linda Cowan and coworkers[2] carried out a study designed to determine which of these two explanations was likely to be the correct one (Fig. 8.8). The researchers identified a population of women who were patients at the Johns Hopkins Hospital Infertility Clinic in Baltimore, Maryland, from 1945 to 1965.

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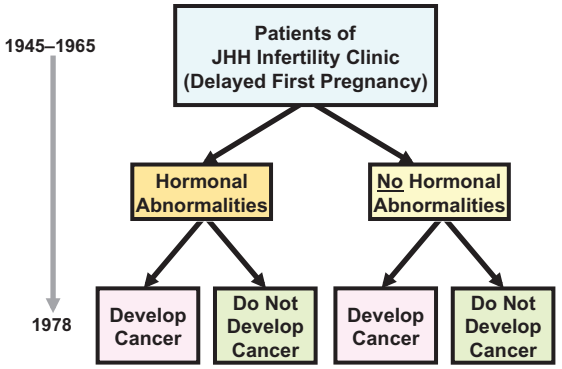

Fig. 8.8 Design of Cowan's retrospective cohort study of breast cancer. *JHH,* Johns Hopkins Hospital. (Data from Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with progesterone deficiency. *Am J Epidemiol.* 1981;114:209–217.)

Because they were patients at this clinic, the subjects, by definition, all had a late age at first pregnancy. In the course of their diagnostic evaluations, detailed hormonal profiles were developed for each woman. The researchers were therefore able to separate the women with an underlying hormonal abnormality, including progesterone deficiency (exposed), from those without such a hormonal abnormality (unexposed) who had another cause of infertility, such as a problem with tubal patency or a partner's low sperm count. Both groups of women were then followed for subsequent development of breast cancer.

How could the results of this study design clarify the relationship between late age at first pregnancy and increased risk of breast cancer? If the explanation for the association of late age at first pregnancy and increased risk of breast cancer is that an early first pregnancy protects against breast cancer, we would not expect any difference in the incidence of breast cancer between the women who have a hormonal abnormality and those who do not (and none of the women would have had an early first pregnancy). However, if the explanation for the increased risk of breast cancer is that the underlying hormonal abnormality predisposes these women to breast cancer, we would expect to find a higher incidence of breast cancer in women with the hormonal abnormality than in those without this abnormality.

The study found that, when the development of breast cancer was considered for the entire group, the incidence was 1.8 times greater in women with hormonal abnormalities than in women without such abnormalities, but the finding was not statistically significant. However, when the occurrence of breast cancer was divided into categories of premenopausal and postmenopausal incidence, women with hormonal abnormalities had a 5.4 times greater risk of premenopausal occurrence of breast cancer (they developed breast cancer earlier); no difference was seen for postmenopausal occurrence of breast cancer. It is not clear whether this lack of a difference in the incidence of postmenopausal breast cancer represents the true absence of a difference or whether it can be attributed to the small number of women in this population who had reached menopause at the time the study was conducted.

What type of study design is this? Clearly, it is a cohort design because it compares exposed and unexposed persons. Furthermore, because the study was carried out in 1978 and the investigator used a roster of patients who had been seen at the Infertility Clinic from 1945 to 1965, it is a historical *nonconcurrent* cohort design.

COHORT STUDIES FOR INVESTIGATING CHILDHOOD HEALTH AND DISEASE

A particularly appealing use of the cohort design is for long-term cohort studies of childhood health and disease. In recent years, there has been increasing recognition that experiences and exposures during fetal life may have long-lasting effects, even into adult life. Infections during pregnancy, as well as exposures to environmental toxins, hormonal abnormalities, or the use of drugs (either medications taken during pregnancy or substances abused during pregnancy), may have potentially damaging effects on the fetus and child, and these agents might have possible effects that last even into adult life. David Barker and his colleagues concluded from their studies that adult chronic disease is biologically programmed in intrauterine life or early infancy.[3] The importance of including a life course approach to the epidemiologic study of chronic disease throughout life has been emphasized.

At Johns Hopkins, we have the Data Analysis Center for the National Institutes of Health (NIH)-sponsored Environmental Influences on Child Health Outcomes (ECHO). The investigation is essentially a cohort of cohorts of women identified during pregnancies or at childbirth of a number of important child outcomes,

including environmental exposures, asthma, and other airway exposures.

In this chapter, we have discussed two types of cohort studies; both have applicability to the study of childhood health. In the first type of cohort study, we start with exposed and unexposed groups. For example, follow-up studies of fetuses exposed to radiation from atomic bombs in Hiroshima and Nagasaki during World War II have provided much information about cancer and other health problems resulting from intrauterine exposure to radiation.[4] The exposure dose was calibrated for the survivors on the basis of the distance that pregnant women were from the point of the bomb drop and the nature of the barriers between that person and the point of the bomb drop. It was then possible to relate the risk of adverse outcome to the expected radiation dose that each person received. Another example is the cohort of pregnancies during the Dutch Famine in World War II.[5] Because the Dutch kept excellent records, it was possible to identify cohorts who were exposed to the severe famine at different times in gestation and to compare them with one another and with an unexposed group.

As discussed earlier in this chapter, in the second type of cohort study, we identify a group before any of its members become exposed or before the exposure has been identified. For example, infants born during a single week in 1946 in Great Britain were followed into childhood and later into adult life. The Collaborative Perinatal Study, begun in the United States in the 1950s, was a multicenter cohort study that followed more than 58,000 children from birth to age 7 years.[6]

Although the potential knowledge to be gained by such studies is very attractive, several challenging questions arise when such large cohort studies of children are envisioned and when such long-term follow-up is planned. Among the questions are the following:

1. At what point should the individuals in the cohort first be identified? When a cohort is initiated at birth and then followed (Fig. 8.9), data on prenatal exposures can be obtained only retrospectively by interview and from relevant records. Therefore, some cohort studies have begun in the prenatal period, at the time when the pregnancy is first identified. However, even when this is done, preconceptual and periconceptual data that may be needed to answer certain questions may only be obtained retrospectively. Therefore, a cohort initiated prior to the time of conception (Fig. 8.10) is desirable for answering many important questions because it permits concurrent gathering of data about exposures at the time of or preceding conception and then in the prenatal and perinatal periods. However, this is generally a logistically difficult and very expensive challenge.
2. Should the cohort be drawn from one center or from a few centers, or should it be a national sample drawn for representativeness (i.e., generalizability) of a national population? Will the findings of studies based on the cohort be broadly generalizable only if the cohort is drawn from a national sample?

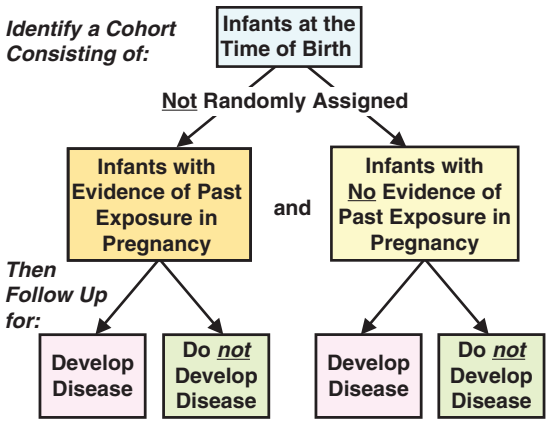

Fig. 8.9 Design of a cohort study to investigate the effects of exposures during pregnancy on disease throughout life: study beginning at birth.

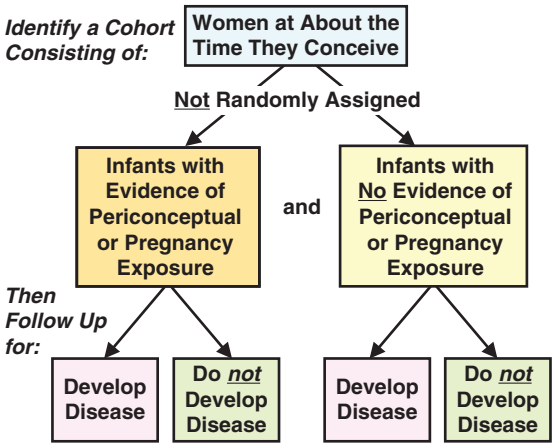

Fig. 8.10 Design of a cohort study to investigate the effects of exposures during pregnancy on disease throughout life: study beginning at about the time of conception.

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The National Children's Study (NCS) was a planned long-term study of 100,000 children and their parents in the United States which was designed to investigate environmental influences on child health and development. The pilot study was initiated in 2009, and only 5,000 children were recruited by 2013 from 40 centers across the United States. Based on the recommendations of an expert panel, the NIH director closed the NCS in 2014. In 2016 the NIH launched a 7-year study called the Environmental Influences on Child Health Outcomes (ECHO), mentioned above, enrolling existing child (and parent in half of the cases) cohorts which will then continue to be followed using harmonized data collection. The resulting "synthetic cohort" (or a cohort of cohorts) should prove far more efficient than the planned NCS proposed cohort.

3. For how long should a cohort be followed? Eaton urged that a cohort should be established at the time of conception and followed into adult life or until death.[7] This approach would help to test Barker's hypothesis regarding the early origins of many chronic diseases. Recalling that federal funding is generally limited to 5 years, this is an impediment to long-term follow-up.

Which hypotheses and how many hypotheses should be tested in the cohort that will be established? A major problem associated with long-term follow-up of large cohorts is that, by the time the cohort has been established and followed for many years, the hypotheses that originally led to the establishment of the cohort may no longer be of sufficient interest or relevance because scientific and health knowledge has changed over time. Furthermore, as new knowledge leads to new hypotheses and to questions that were not originally anticipated when the study was initiated, data on the variables needed to test such new hypotheses and to answer such new questions may not be available in the data originally collected. An example from HIV/AIDS research illustrates these issues. In the early 1980s, when clusters of men were identified who had rare malignancies associated with compromised immune function, later to be defined as HIV/AIDS, the NIH launched the Multicenter AIDS Cohort Study in 1983 and enrolled the first participants in four US cities in 1984.[8] The goal was to identify risk factors for this viral disease and to elucidate the natural history of the disease. With the advent of highly active antiretroviral therapy in 1996, virtually all study participants who were already infected were then placed on treatment, and their immune systems were reconstituted. How then could the natural history of a treated infection remain relevant? Was there any use in continuing to follow this cohort? Indeed, a vast number of new, relevant questions unfolded, chief among them becoming what is the impact of long-term antiretroviral therapy treatments upon natural aging and the incidence of chronic diseases (cancer, cardiovascular disease, and diabetes, among others)?[9] Furthermore, new genetic tests have been discovered over the past 15 years that provide new insights into why some participants do better than others on treatment.[10] It must be emphasized that cohort studies whose participants are examined periodically, such as the Atherosclerosis Risk in Communities (ARIC) study,[11] allow evaluation of new hypotheses based on information that is collected in follow-up examinations.

POTENTIAL BIASES IN COHORT STUDIES

A number of potential biases must be either avoided or taken into account in conducting cohort studies. Discussions of biases in relation to case-control studies were presented earlier; bias in relation to causal inference will be presented later. The definitions used for many types of biases often overlap, and in the interest of clarity, two major categories are commonly used: *selection bias* and *information bias*. There are numerous mechanisms by which each of these two biases may occur in research studies.

Selection Biases

Nonparticipation and nonresponse can introduce major biases that can complicate the interpretation of the study findings. If participants refuse to join a cohort, might their characteristics differ sufficiently from those who consent to enroll, and might these differences lead to misguided inferences regarding exposures to outcomes? For example, if those who refuse to join a study are more likely to smoke than those who consent to participate, would our estimate of the effect of smoking on the disease outcome be biased? If smokers who refuse participation are more likely to develop the disease than those who participate, the impact would be to diminish the association toward the null. Similarly, loss to follow-up can be a serious problem: If people with the disease are selectively lost to follow-up, and those lost to

follow-up differ from those not lost to follow-up, the incidence rates calculated in the exposed and unexposed groups will clearly be difficult to interpret.

Information Biases

1. If the quality and extent of information obtained is different for exposed persons than for the unexposed persons, a significant bias can be introduced. This is particularly likely to occur in historical cohort studies, in which information is obtained from past records. As we will discuss next in connection with randomized trials, in any cohort study, it is essential that the quality of the information obtained be comparable in both exposed and unexposed individuals.
2. If the person who decides whether the disease has developed in each subject also knows whether that subject was exposed, and if that person is aware of the hypothesis being tested, that person's judgment as to whether the disease developed may be biased by that knowledge. This problem can be addressed by "masking" the person who is making the disease assessment and also by determining whether this person was, in fact, aware of each subject's exposure status.
3. As in any study, if the epidemiologists and statisticians who are analyzing the data have strong preconceptions, they may unintentionally introduce their biases into their data analyses and into their interpretation of the study findings.

WHEN IS A COHORT STUDY WARRANTED?

Fig. 8.11A to C reviews the basic steps in a cohort study, beginning with identifying an exposed group and an unexposed group (see Fig. 8.11A). We then ascertain the rate of development of disease (incidence) in both the exposed and the unexposed groups (see Fig. 8.11B). If the exposure is associated with disease, we would expect to find a greater incidence rate of disease in the exposed group than in the unexposed group, as shown schematically in Fig. 8.11C.

Ideally, to carry out a cohort study, we must have some idea of which exposures are suspected *a priori* as possible causes of a disease and are therefore worth investigating. Consequently, a cohort study is indicated when evidence suggests an association of a disease with a certain exposure or exposures (evidence obtained from either clinical observations or case-control or other types of studies). Often, we collect biologic specimens at study baseline (enrollment), allowing testing of these samples at some time in the future, often when new test methods are developed and/or new hypotheses are generated. As an example, Dr. George Comstock collected serum specimens at the time of a community assessment in the 1960s in Washington County, Maryland. Decades later, these specimens were tested for "clues" to the development of cancer. Results from the Campaign Against Cancer and Heart Disease (CLUE II) cohort study that Dr. Comstock founded showed that high serum cholesterol increases the risk of high-grade prostate cancer and subsequently supports the hypothesis that cholesterol lowering is a potential mechanism by which statins, cholesterol-lowering medications, could have anticancer effects.[12]

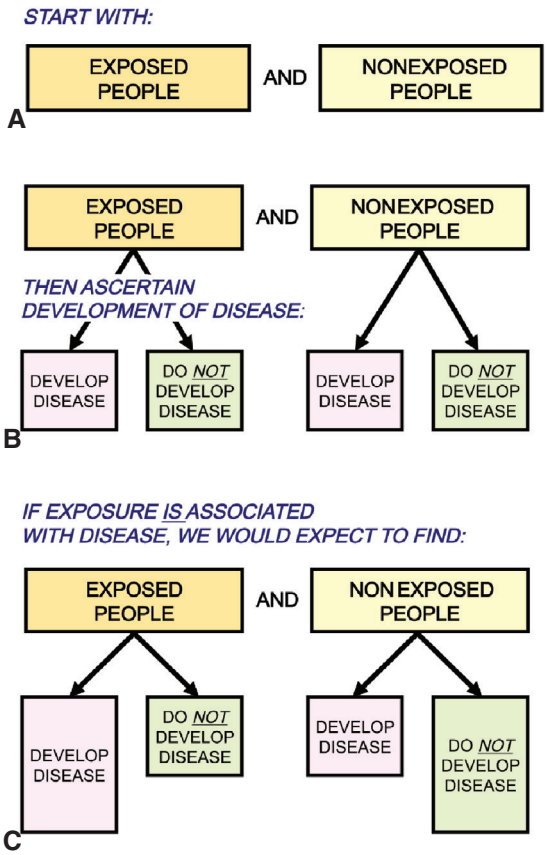

Fig. 8.11 Design of a cohort study. (A) Starting with exposed and unexposed groups. (B) Measuring the development of disease in both groups. (C) Expected findings if the exposure is associated with disease.

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Because cohort studies often involve follow-up of populations over a long period, the cohort approach is particularly attractive when we can minimize attrition (losses to follow-up) of the study population. Consequently, such studies are generally easier to conduct when the interval between the exposure and the development of disease is short. An example of an association in which the interval between exposure and outcome is short is the relationship between rubella infection during pregnancy and the development of congenital malformations in the offspring.

CASE-CONTROL STUDIES BASED WITHIN A DEFINED COHORT

In recent years, considerable attention has focused on whether it is possible to take advantage of the benefits of both case-control and cohort study designs by combining some elements of both into a single study. The resulting combined study is in effect a hybrid design in which a case-control study is initiated within a cohort study. The general design is shown schematically in Fig. 8.12.

In this type of study, a population is identified and followed over time. At the time the population is identified, baseline data are obtained from records or interviews, from blood or urine tests, and in other ways. The population is then followed for a period of years. For most of the diseases that are studied, a relatively small percentage of study participants manifest the disease, whereas most do not. As seen in Fig. 8.12, a case-control study is then carried out using as cases persons in whom the disease developed and using as controls a sample of those in whom the disease did not develop.

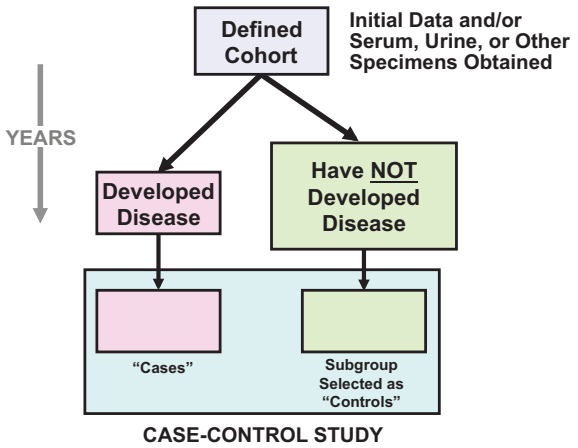

Fig. 8.12 Design of a case-control study initiated within a cohort.

Such cohort-based case-control studies can be divided into two types, largely based on the approach used for selecting the controls. These two types of studies are called *nested case-control studies* and *case-cohort studies*.

Nested Case-Control Studies

In *nested case-control studies* the controls are a sample of individuals who are at risk for the disease *at the time each case of the disease develops*. This is shown schematically in Fig. 8.13A to I.

Fig. 8.13A shows the starting point as a defined cohort of individuals. Some of them develop the disease in question, but most do not. In this hypothetical example, the cohort is observed over a 5-year period. During this time, five cases develop—one case after 1 year, one after 2 years, two after 4 years, and one after 5 years.

Let us follow the sequence of steps over time. Fig. 8.13B to I shows the time sequence in which the cases develop after the start of observations. At the time each case or cases develop, the same number of controls is selected. The solid arrows on the left side of the figure denote the appearance of cases of the disease, and the dotted arrows on the right side denote the selection of controls who are disease free but who are at risk of developing the disease in question at the time the case develops the disease. Fig. 8.13B shows case #1 developing after 1 year, and Fig. 8.13C shows control #1 being selected at that time. Fig. 8.13D shows case #2 developing after 2 years, and Fig. 8.13E shows control #2 being selected at that time. Fig. 8.13F shows cases #3 and #4 developing after 4 years, and Fig. 8.13G shows controls #3 and #4 being selected at that time. Finally, Fig. 8.13H shows the final case (#5) developing after 5 years, and Fig. 8.13I shows control #5 being selected at this point.

Fig. 8.13I is also a summary of the design and the final study populations used in the nested case-control study. At the end of 5 years, five cases have appeared, and at the times the cases appeared a total of five controls were selected for study. In this way, the cases and controls are, in effect, matched on calendar time and length of follow-up. Because a control is selected each time a case develops, a control who is selected early in the study could later develop the disease and become a case in the same study. Practically, a nested case-control study is more involved than in this schematic scenario!

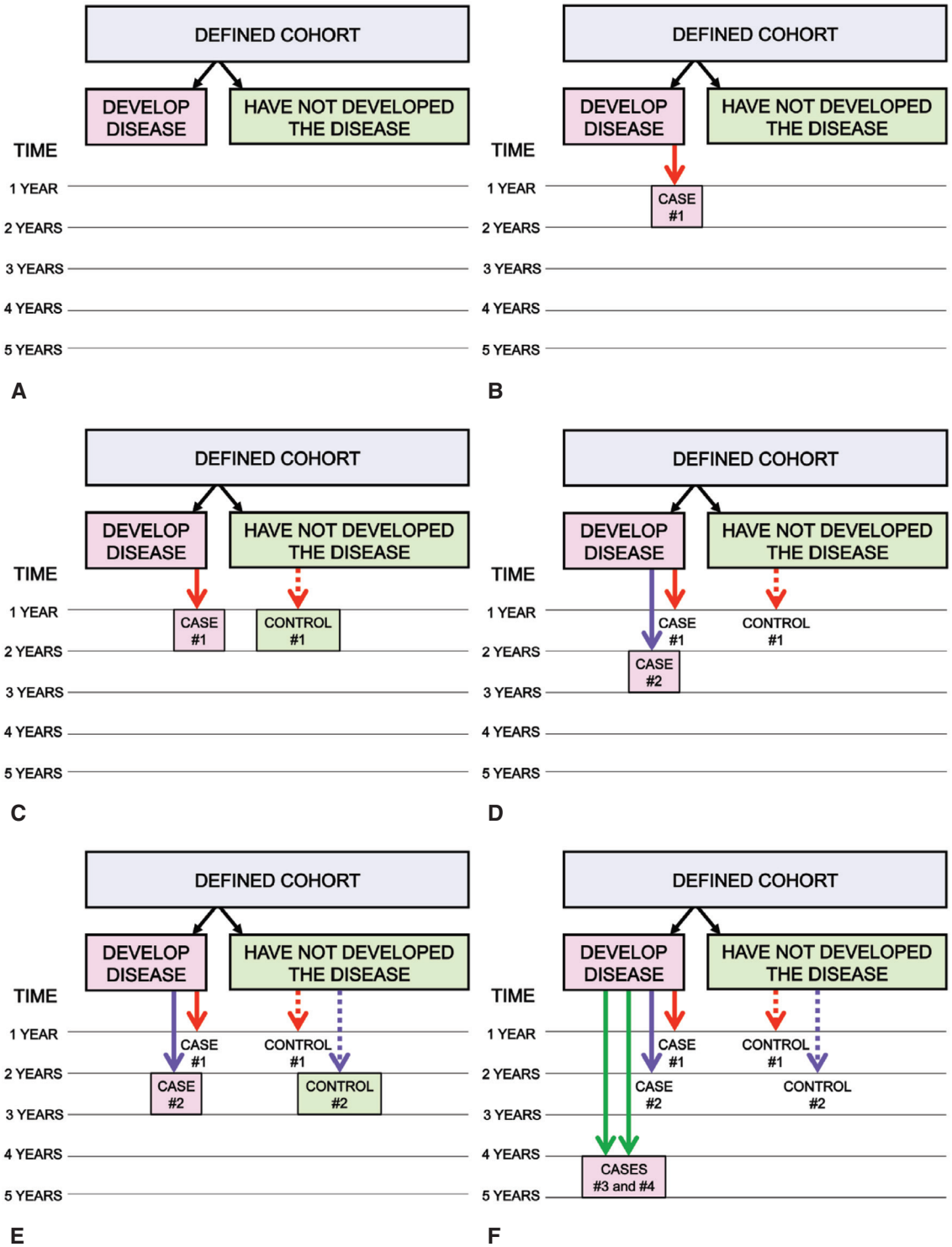

Fig. 8.13 **(A–I)** Design of a hypothetical nested case-control study: steps in selecting cases and controls.

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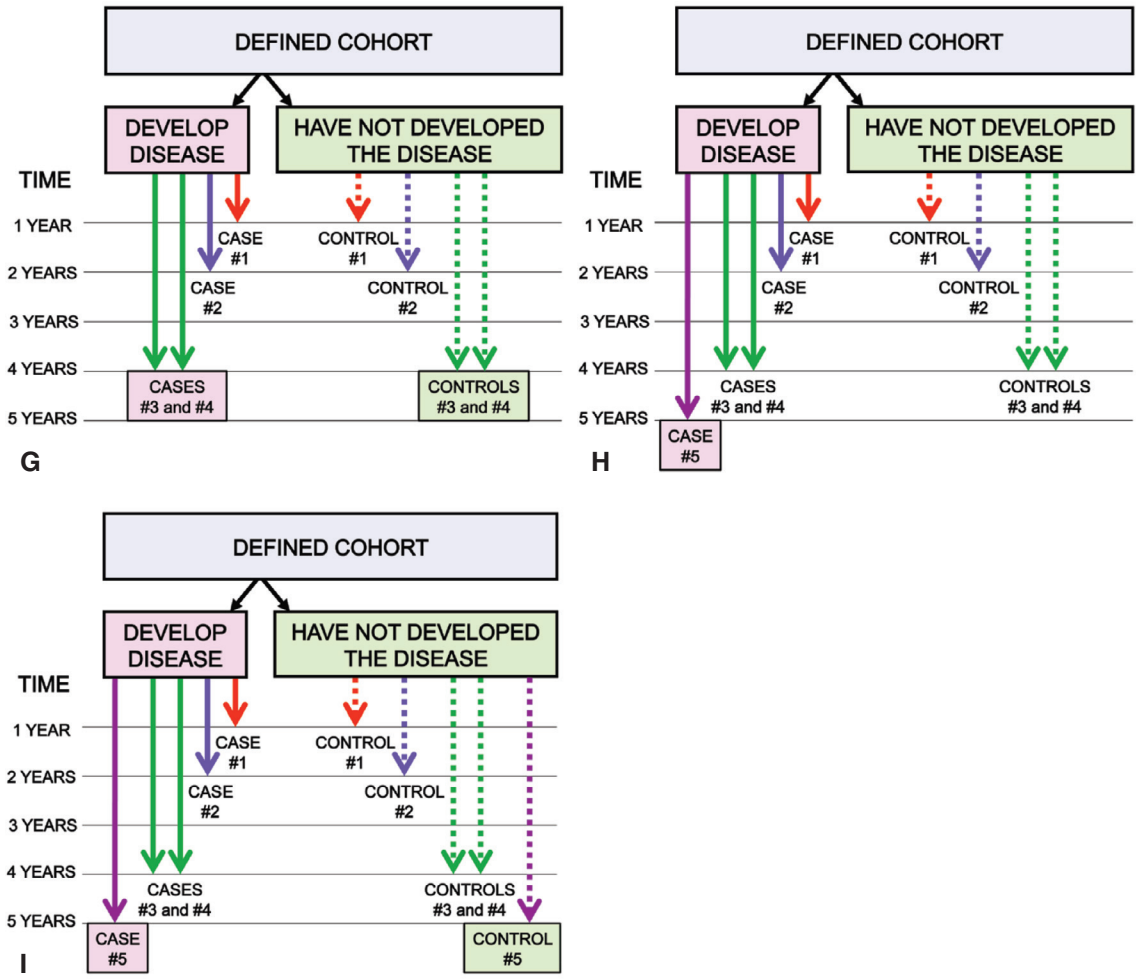

Fig. 8.13, cont'd

Case-Cohort Studies

The second type of cohort-based case-control study is the *case-cohort design* seen in Fig. 8.14. In the hypothetical case-cohort study seen here, cases develop at the same times that were seen in the nested case-control design just discussed, but the controls are randomly chosen from the defined cohort with which the study began. This subset of the full cohort is called the subcohort. An advantage of this design is that because controls are not individually matched to each case, it is possible to study different diseases (different sets of cases) in the same case-cohort study using the same cohort for controls. In this design, in contrast to the nested case-control design, cases and controls are not matched on calendar time and length of follow-up; instead, exposure is characterized for the subcohort. This difference in study design needs to be considered in analyzing the study results.

Advantages of Embedding a Case-Control Study in a Defined Cohort

What are the advantages of conducting a case-control study in a defined cohort? First, because interviews are completed or certain blood or urine specimens are obtained at the beginning of the study (at baseline), the data are obtained before any disease has developed. Consequently, the problem of possible recall bias discussed earlier in this chapter is eliminated. Second, if

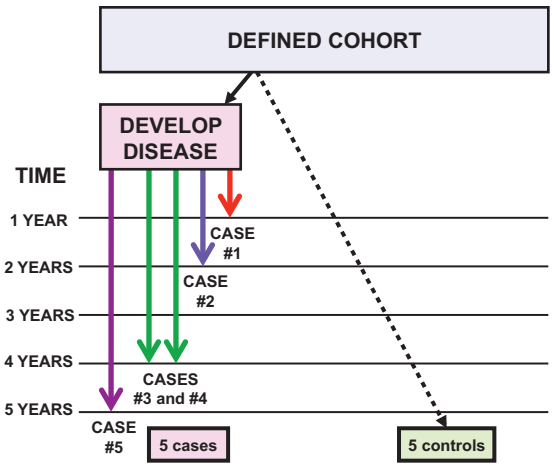

Fig. 8.14 Design of a hypothetical case-cohort study: steps in selecting cases and controls.

abnormalities in biologic characteristics, such as laboratory values, are identified because the specimens were obtained years before the development of clinical disease, it is more likely that these findings represent risk factors or other premorbid characteristics than a manifestation of early, subclinical disease. When such abnormalities are found in the traditional case-control study, we do not know whether they preceded the disease or were a result of the disease, particularly when the disease has a long subclinical (asymptomatic) phase, such as prostate cancer and chronic lymphocytic leukemia. Third, such a study is often more economical to conduct. One might ask, why perform a case-control study within a defined cohort? Why not perform a regular *concurrent* cohort study? The answer is that in a cohort study of, say, 10,000 people, laboratory analyses of all the specimens obtained would have to be carried out, often at great cost, to define *exposed and unexposed* groups. However, in a case-control study within the same cohort, the specimens obtained initially are frozen or otherwise stored for prosperity. Only after the disease has developed in some subjects is a case-control study begun and the specimens from the relatively small number of people who are included in the case-control study are thawed and tested. Laboratory tests would not need to be performed on all 10,000 people in the original cohort. Thus, the laboratory burden and costs are dramatically reduced.

Finally, in both nested case-control and case-cohort designs, cases and controls are derived from the same original cohort, so there is likely to be greater comparability between the cases and the controls than one might ordinarily find in a traditional case-control study. For all these reasons, the cohort-based case-control study is an extremely efficient and valuable type of study design.

CONCLUSION

Several considerations can make the cohort design impractical. Often, strong evidence does not exist to justify mounting a large and expensive study for in-depth investigation of the role of a specific risk factor in the etiology of a disease. Even when such evidence is available, a cohort of exposed and unexposed persons often cannot be identified easily. In general, we do not have access to appropriate past records or other sources of data that enable us to conduct a *nonconcurrent* cohort study; as a result, a long study is required because of the need for extended follow-up of the population after exposure. Furthermore, many of the diseases that are of interest today occur at very low rates. Consequently, very large cohorts must be enrolled in a study to ensure that enough cases develop by the end of the study period to permit valid analyses and conclusions. Furthermore, even if a relationship is identified between an exposure and a disease from a cohort study, the next step in is to assess whether preventing or treating such exposure (if harmful) is associated with a lower incidence of the disease. This will be discussed in detail in Chapters 10 and 11 when we present the clinical trials designs.

In view of these considerations, an approach other than a cohort design—one that will surmount many of these difficulties—is often needed, such as the case-control study design. Later, we discuss the use of these study designs in estimating increased risk associated with an exposure.

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REVIEW QUESTIONS FOR CHAPTER 8

1. *In cohort studies of the role of a suspected factor in the etiology of a disease, it is essential that:*
- **a.** There be equal numbers of persons in both study groups
- **b.** At the beginning of the study, those with the disease and those without the disease have equal risks of having the factor
- **c.** The study group with the factor and the study group without the factor be representative of the general population
- **d.** The exposed and unexposed groups under study be as similar as possible with regard to possible confounding factors
- **e.** Both *b* and *c*

2. *Which of the following is not an advantage of a concurrent cohort study?*
- **a.** It usually costs less than a case-control study
- **b.** Precise measurement of exposure is possible
- **c.** Incidence rates can be calculated
- **d.** Recall bias is minimized compared with a case-control study
- **e.** Many disease outcomes can be studied simultaneously

3. *Nonconcurrent cohort studies are characterized by all of the following except:*
- **a.** The study groups are exposed and unexposed
- **b.** Incidence rates may be computed
- **c.** The required sample size is smaller than that needed for a *concurrent* cohort study
- **d.** The required sample size is similar to that needed for a *concurrent* cohort study
- **e.** They are useful for rare exposures

4. *A major problem resulting from the lack of randomization in a cohort study is:*
- **a.** The possibility that a factor that led to the exposure, rather than the exposure itself, might have caused the disease
- **b.** The possibility that a greater proportion of people in the study may have been exposed
- **c.** The possibility that a smaller proportion of people in the study may have been exposed
- **d.** That, without randomization, the study may take longer to carry out
- **e.** Planned crossover is more likely

5. *In a cohort study, the advantage of starting by selecting a defined population for study before any of its members become exposed, rather than starting by selecting exposed and unexposed individuals, is that:*
- **a.** The study can be completed more rapidly
- **b.** A number of outcomes can be studied simultaneously
- **c.** A number of exposures can be studied simultaneously
- **d.** The study will cost less to carry out
- **e.** *a* and *d*

6. *In 2010, investigators were interested in studying early-adult obesity as a risk factor for cancer mortality. The investigators obtained physician health reports on*

students who attended the University of Glasgow between 1948 and 1968. These reports included records of the students' heights and weights at the time they attended the university. The students were then followed through 2010. Mortality information was obtained using death certificates. This study can best be described as a:

a. Nested case-control
b. Cross-sectional
c. *Concurrent* cohort
d. *Nonconcurrent* cohort
e. Population-based case-control

7. *From 1983 to 1988, blood samples were obtained from 3,450 HIV-negative men in the Multicenter AIDS Cohort Study (MACS) and stored in a national repository. In 2010 a researcher was interested in examining the association between levels of inflammation and HIV infection. Of the 3,450 men, 660 men were identified as HIV-infected cases. The researcher investigated the association between C-reactive protein (CRP) and HIV infection among these 660 cases and 660 controls, matched to the cases by age and ethnicity, who did not become infected with HIV. The researcher used the stored blood samples to measure the serum level of CRP, a marker of systemic inflammation. The study initiated in 2010 is an example of a:*

a. Nested case-cohort study
b. Nested case-control study
c. *Nonconcurrent* cohort study
d. Cross-sectional study
e. Randomized clinical trial

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9

Comparing Cohort and Case-Control Studies

At this point in our discussion, we will review some of the material that has been covered to this point in Section II. Because the presentation proceeds in a stepwise manner, it is important to understand and synthesize what has been discussed thus far.

First, let's compare the designs of cohort and case-control studies, as seen in Fig. 9.1. The important point that distinguishes between these two types of study designs is that, in a cohort study, exposed and unexposed persons are compared and, in a case-control study, persons with the disease (cases) and without the disease (controls) are compared (Fig. 9.2A). In cohort studies, we compare the incidence of disease in exposed and in unexposed individuals, and in case-control studies, we compare the proportions who have the exposure of interest in people with the disease and in people without the disease (see Fig. 9.2B).

Table 9.1 presents a detailed comparison of prospective cohort, retrospective (historical) cohort, and case-control study designs. If the reader has followed the discussion in Section II to this point, the entries in the table should be easy to understand.

When we begin a cohort study with exposed and unexposed groups, we can study only the specific exposure that distinguishes one group from the other. However, as shown in Fig. 9.3, we can study multiple outcomes or diseases in relation to the exposure of interest. Most cohort studies start with exposed and unexposed individuals. Less common is the situation where we start with a defined population in which the study population is selected on the basis of a factor not related to exposure, such as place of residence, and some members of the cohort become exposed, and others are not exposed over time (Fig. 9.4). In a cohort study that starts with a defined population, it is possible to study multiple exposures. Thus, for example, in the Framingham Study, it was possible to study many exposures, including weight, blood pressure, cholesterol level, smoking, and physical activity among the participating individuals residing in Framingham, Massachusetts.

In cohort studies, incidence in both exposed and unexposed groups *can* be calculated, and we can therefore directly calculate the relative risk. Prospective cohort studies minimize the potential for recall and other bias in assessing the exposure and have greater validity of the exposure assessments. However, in retrospective cohort studies, which require data from the past, these problems may be significant. Cohort studies are desirable when the exposure of interest is rare. In a case-control design, we are unlikely to identify a sufficient number of exposed persons when we are dealing with a rare exposure. In prospective cohort studies in particular, we are likely to have better data on the temporal relationship between exposure and outcome (i.e., did the exposure precede the outcome?) Among the disadvantages of cohort studies is that they usually require large populations, and, in general, prospective cohort studies are especially expensive to carry out because of the infrastructure required to follow-up a large population over time. A greater potential bias for assessing the outcome is present in cohort studies than in case-control studies. Finally, cohort studies often become impractical when the disease under study is rare.

As seen in Table 9.1, traditional case-control studies have a number of advantages. They are relatively inexpensive and require a relatively small number of subjects for study. They are desirable when the disease occurrence is rare, because if a cohort study were performed in such a circumstance, a tremendous number of people would have to be followed to generate enough people with the disease for study. As seen in Fig. 9.5, in a case-control study, because we begin with cases and controls, we are able to study more than one

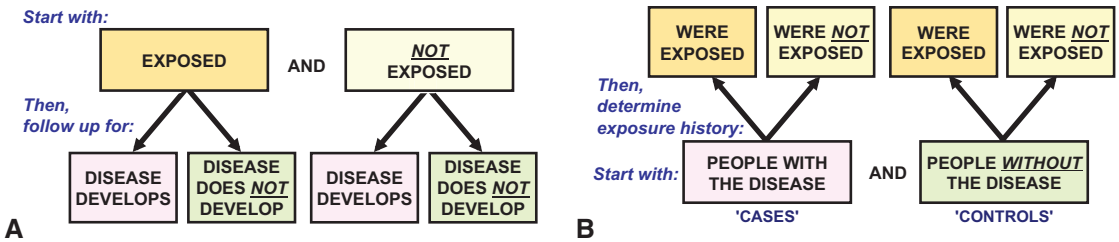

Fig. 9.1 Design of cohort and case-control studies. **(A)** Cohort study. **(B)** Case-control study.

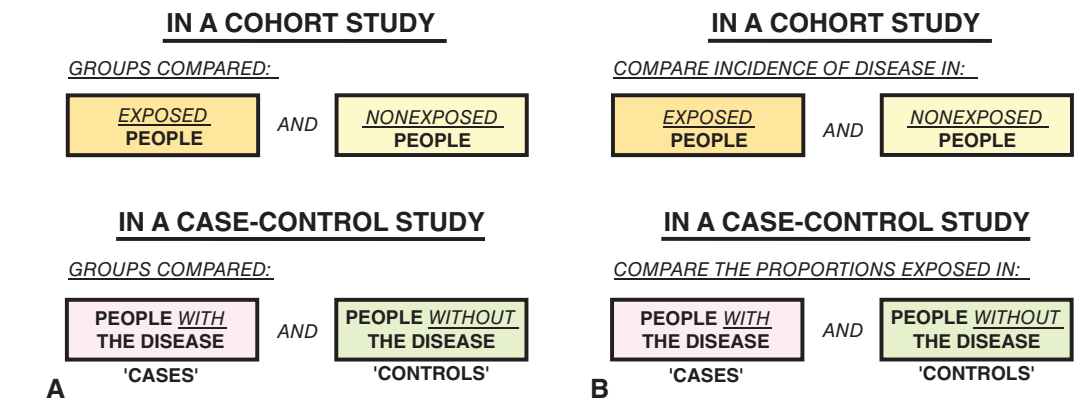

Fig. 9.2 Comparison of cohort and case-control study designs. **(A)** Groups compared. **(B)** Outcome measurements.

possible etiologic factor and to explore interactions among the factors.

Because case-control studies often require data about past events or exposures, they are often encumbered by the difficulties encountered in using such data (including a potential for recall bias). Furthermore, as has been discussed in some detail, selection of an appropriate control group is one of the most difficult methodologic problems encountered in epidemiology. In addition, in most case-control studies, we cannot calculate disease incidence in either the total population or the exposed and unexposed groups without some supplemental information.

The case-control design within a defined cohort combines elements of both cohort and case-control studies and offers a number of advantages. The possibility of recall bias is eliminated because the data on exposure are obtained before the disease develops. Exposure data are more likely to represent the pre-illness state because they are obtained years before clinical illness is diagnosed. Finally, the costs are lower than with a cohort study because laboratory tests need to be done only on specimens from subjects who are later chosen as cases or controls; that is, we need to selectively do laboratory tests only on a subset of the overall cohort, thereby yielding considerable cost savings.

In addition to the cohort and case-control study designs, we have discussed the cross-sectional study design, in which data on both exposure and disease outcomes are collected simultaneously from each subject. The data from a cross-sectional study can be analyzed by comparing the prevalence of disease in exposed individuals with that in unexposed individuals or by comparing the prevalence of exposure in persons with the disease with that of persons without the disease. Although cross-sectional data are often obtained from representative surveys and can be very useful, they usually do not permit the investigator to determine the temporal relationship between exposure and the development of disease. As a result, their value for deriving causal inferences is somewhat limited. However, they can provide important directions for further research using cohort, case-control, and case-control study designs within a cohort.

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TABLE 9.1 Comparisons of Cohort and Case-Control Studies

	COHORT STUDIES		
	Prospective	**Retrospective**	**Case-Control Studies**
A. Study group	Exposed persons: $(a + b)$	Exposed persons: $(a + b)$	Persons with the disease (cases): $(a + c)$
B. Comparison group	Nonexposed persons: $(c + d)$	Nonexposed persons: $(c + d)$	Persons without disease (controls): $(b + d)$
C. Outcome measurements	Incidence in the exposed	Incidence in the exposed	Proportion of cases exposed
	$\frac{a}{a+b}$	$\frac{a}{a+b}$	$\frac{a}{a+c}$
	and	and	and
	Incidence in the nonexposed	Incidence in the nonexposed	Proportion of controls exposed
	$\frac{c}{c+d}$	$\frac{c}{c+d}$	$\frac{b}{b+d}$
D. Measures of risk	Absolute risk	Absolute risk	—
	Relative risk	Relative risk	—
	Odds ratio	Odds ratio	Odds ratio
	Attributable risk	Attributable risk	Attributable risk[a]
E. Temporal relationship between exposure and disease	Easy to establish	Sometimes hard to establish	Sometimes hard to establish
F. Multiple associations	Possible to study associations of an exposure with several diseases[b]	Possible to study associations of an exposure with several diseases[b]	Possible to study associations of a disease with several exposures or factors
G. Time required for the study	Generally long because of need to follow the subjects	May be short	Relatively short
H. Cost of study	Expensive	Generally less expensive than a prospective cohort study	Relatively inexpensive
I. Population size needed	Relatively large	Relatively large	Relatively small
J. Potential bias	Mainly assessment of outcome	Susceptible to bias both in assessment of exposure and assessment of outcome	Assessment of exposure
K. Best when	Exposure is rare	Exposure is rare	Disease is rare
	Disease is frequent among exposed	Disease is frequent among exposed	Exposure is frequent among persons with disease
L. Problems	Selection of nonexposed comparison group often difficult Changes over time in criteria and methods	Selection of nonexposed comparison group often difficult Changes over time in criteria and methods	Selection of appropriate controls often difficult Incomplete information on exposure

[a]Additional information must be available.
[b]It is also possible to study multiple exposures when the study population is selected on the basis of a factor unrelated to the exposure.

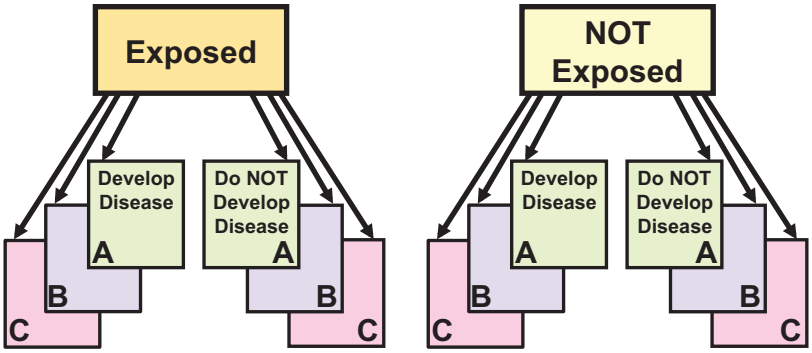

Fig. 9.3 In a cohort study that starts with an exposed group and a nonexposed group, we can study multiple outcomes but only one exposure.

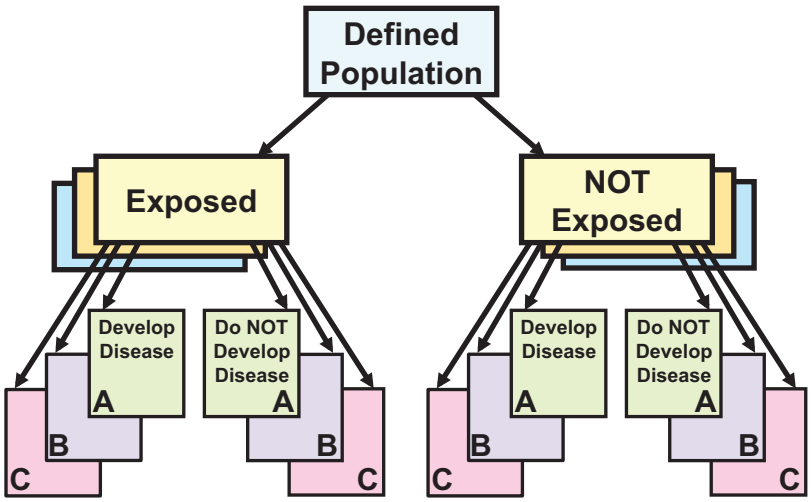

Fig. 9.4 In a cohort study that starts with a defined population, we can study both multiple exposures and multiple outcomes.

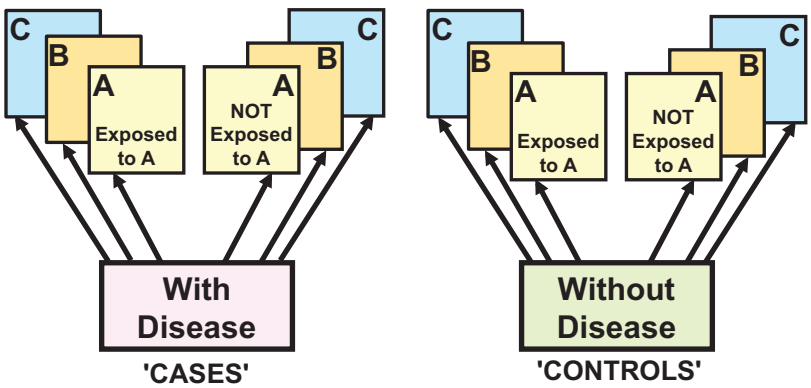

Fig. 9.5 In a case-control study which starts by identifying cases and controls, we can study multiple exposures but only one outcome.

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10

Assessing Preventive and Therapeutic Interventions: Randomized Trials

All who drink of this treatment recover in a short time,
Except those whom it does not help, who all die,
It is obvious, therefore, that it fails only in incurable cases.

—Galen[1] (129–c. 199 CE)

LEARNING OBJECTIVES

- To describe the important elements of randomized trials.
- To define the purpose of randomization and of masking.
- To introduce design issues related to randomized trials, including stratified randomization, planned and unplanned crossovers, and factorial design.
- To illustrate the problems posed by noncompliance in randomized trials.

Some ways of quantifying the natural history of disease and of expressing disease prognosis were discussed in Chapter 6. Our objective, both in clinical practice and in public health, is to modify the natural history of a disease so as to prevent or delay death or disability and to improve the health of the patient or the population. The challenge is to select the best available preventive or therapeutic interventions to achieve this goal. To do so, we need to carry out studies that determine whether these interventions work (efficacy or effectiveness) and are safe. The randomized trial is considered the ideal design for evaluating both the efficacy and the side effects of new forms of intervention.

The notion of using a rigorous methodology to assess the efficacy of new drugs, or of any new modalities of care, is not recent. In 1883, Sir Francis Galton, the British anthropologist, wrote as follows:

> *It is asserted by some, that men possess the faculty of obtaining results over which they have little or no direct personal control, by means of devout and earnest prayer, while others doubt the truth of this assertion. The question regards a matter of fact, that has to be determined by observation and not by authority; and it is one that appears to be a very suitable topic for statistical inquiry. ... Are prayers answered, or are they not? ... [D]o sick persons who pray, or are prayed for, recover on the average more rapidly than others?*[2]

As with many pioneering ideas in science and medicine, many years were to pass before this suggestion was actually implemented. In 1965, Joyce and Welldon reported the results of a randomized double-blind trial of the efficacy of prayer.[3] The findings of this study did not indicate that patients who were prayed for derived any special benefits from that prayer. However, a more recent study by Byrd[4] evaluated the effectiveness of intercessory prayer in a coronary care unit population using a randomized double-blind protocol. The findings from this study suggested that prayer had a beneficial therapeutic effect. *Which is correct?*

In this chapter and the one following, we discuss study designs that can be used for evaluating approaches to treatment and prevention and focus on the

use of the randomized trial. Although the term *randomized clinical trial* is often used together with its acronym, RCT, the randomized trial design also has major applicability to studies outside the clinical setting, such as community-based trials. For this reason, we use the term *randomized trial.* To facilitate our discussion, reference is generally made to treatments and drugs; the reader should bear in mind that the principles described apply equally to assess new programs for screening and early detection, to compare different approaches to prevention, or new ways of organizing and delivering health services.

Trials are essentially experiments that are under the control of the investigator. Compare this with observational studies reviewed in Chapter 7, where the investigator watches what unfolds but does not interfere.

Suggestions of many of the elements that are important to randomized trials can be seen in many anecdotal descriptions of early trials. In a review of the history of clinical trials, Bull described an unintentional trial conducted by Ambroise Paré (1510–1590), a leading figure in surgery during the Renaissance.[5] Paré lived at a time when the standard treatment for war wounds was the application of boiling oil. In 1537 Paré was responsible for the treatment of the wounded after the capture of the castle of Villaine. The wounded were so numerous that, he says:

> *At length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at my ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil, dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded.*

Although this was not a randomized trial, it was a form of unplanned trial, which has been carried out many times when a therapy thought to be the best available has been in short supply and has not been available for all of the patients who needed it.

A planned trial was described by the Scottish surgeon James Lind in 1747.[6] Lind became interested in scurvy, which killed thousands of British seamen each year. He was intrigued by the story of a sailor who had developed scurvy and had been put ashore on an isolated island, where he subsisted on a diet of grasses and then recovered from the scurvy. Lind conducted an experiment, which he described as follows:

> *I took 12 patients in the scurvy on board the Salisbury at sea. The cases were as similar as I could have them ... they lay together in one place and had one diet common to them all. Two of these were ordered a quart of cider per day. ... Two others took 25 gutts of elixir vitriol. ... Two others took two spoonfuls of vinegar. ... Two were put under a course of sea water. ... Two others had two oranges and one lemon given them each day. ... Two others took the bigness of nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of 6 days fit for duty. ... The other ... was appointed nurse to the rest of the sick.*

Interestingly, the idea of a dietary cause of scurvy proved unacceptable in Lind's day. Only 47 years later did the British Admiralty allow the experiment to be repeated—this time on an entire fleet of ships. The results were so dramatic that, in 1795, the Admiralty made lemon juice a required part of the standard diet of British seamen and later changed this to lime juice. Scurvy essentially disappeared from British sailors, who, even today, are referred to as "limeys."

Randomized trials can be used for many purposes. They can be used for evaluating new drugs and other treatments of disease, including lifestyle interventions and tests of new health and medical care technology. The basic design of a randomized trial is shown in Fig. 10.1.

We often begin with a defined population in which participants are randomized to receive either a new treatment or the current treatment (often referred to as "usual care" or "standard of care"), and we then follow the subjects in each group to see how many are improved in the new treatment group compared with how many are improved in the current treatment group. If the new treatment is associated with a better outcome, we would expect to find better outcomes in more of the

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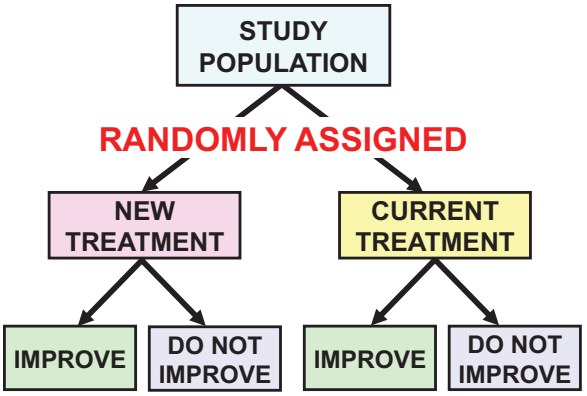

Fig. 10.1 Design of a randomized trial.

new treatment group than in the current treatment group.

We may choose to compare two groups receiving different therapies, or we may compare more than two groups. Although at times a new treatment may be compared with no treatment, often a decision is made not to use an untreated group. For example, if we wanted to evaluate a newly developed therapy for acquired immunodeficiency syndrome (AIDS), would we be willing to have a group of AIDS patients in our study who were untreated? The answer is clearly no; we would compare the newly developed therapy with a currently recommended regimen, which would clearly be much better than no therapy at all. Perhaps the use of an untreated group may only be justified if there are not approved therapies for the disease being studied. In this case, a "placebo" can be used.

Let us now turn to some of the issues that must be considered in the design of randomized trials. Chief among them is specification of the study "arms," or treatments. These must be clearly stated with criteria for their measurement, as well as the duration of the treatments and how long the study will last. First, let's start with who is eligible to be studied.

SELECTION OF SUBJECTS

The criteria for determining who will or will not be included in the study must be spelled out with great precision and *in writing before the study is begun.* Similar to a study hypothesis, these should be *prespecified* (also called *a priori*) at the time of the study design planning. An excellent test of the adequacy of these written criteria is to ask: If we have spelled out our criteria in writing and someone not involved in the study walks in off the street and applies our criteria to the same population, will that person select the same subjects whom we would have selected? There should be no element of subjective decision-making on the part of the investigator in deciding who is included or not included in the study. Any study procedure must in principle be replicable by others, just as is the case with laboratory experiments. Clearly, this is easier said than done, because in randomized trials we are often dealing with relatively large populations. The principle is nevertheless important, and the selection criteria must therefore be precisely stated.

ALLOCATING SUBJECTS TO TREATMENT GROUPS WITHOUT RANDOMIZATION

Before discussing the process of randomization, let us ask whether there might be some alternatives to randomization that could be used.

Studies Without Comparison

The first possible alternative is the *case study* or *case series* (as was presented in Chapter 7). In this type of study, no comparison is made with an untreated group or with a group that is receiving some other treatment. The following story was told by Dr. Earl Peacock when he was chairman of the Department of Surgery at the University of Arizona:

> *One day when I was a junior medical student, a very important Boston surgeon visited the school and delivered a great treatise on a large number of patients who had undergone successful operations for vascular reconstruction. At the end of the lecture, a young student at the back of the room timidly asked, "Do you have any controls?" Well, the great surgeon drew himself up to his full height, hit the desk, and said, "Do you mean did I not operate on half of the patients?" The hall grew very quiet then. The voice at the back of the room very hesitantly replied, "Yes, that's what I had in mind." Then the visitor's fist really came down as he thundered, "Of course not. That would have doomed half of them to their death." God, it was quiet then, and one could scarcely hear the small voice ask, "Which half?"*[7]

The issue of comparison is important because we want to be able to derive a causal inference regarding the

relationship of a treatment and subsequent outcome. The problem of inferring a causal relationship from a sequence of events without any comparison is demonstrated in a story cited by Ederer.[8]

> *During World War II, rescue workers, digging in the ruins of an apartment house blown up in the London blitz, found an old man lying naked in a bathtub, fully conscious. He said to his rescuers, "You know, that was the most amazing experience I ever had. When I pulled the plug and the water started down the drain, the whole house blew up."*

The problem exemplified by this story is: If we administer a drug and the patient improves, can we attribute the improvement to the administration of that drug? Professor Hugo Muensch of Harvard University articulated his Second Law: "*Results can always be improved by omitting controls*."[9]

For example, in June 2020, in the first peak of the COVID-19 pandemic, results of a study were published,[10] titled "Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients." The paper was instrumental in the Food and Drug Administration (FDA)´s decision to issue the Emergency Use Authorization for convalescent plasma for hospitalized COVID-19 patients. The authors stated that the objective of their study was to provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized COVID-19 patients. They analyzed data from a convenience sample of the US FDA Expanded Access Program for COVID-19 convalescent plasma in which ALL of the 20,000 hospitalized patients with COVID-19 were transfused with convalescent plasma. That was a critical flaw of the study—the absence of a controlled comparison group who were not exposed to convalescent plasma. Despite this, the authors concluded that "*These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.*" Unfortunately, this was a conclusion that did not align with the kind of evidence that came from such a single arm non-controlled study and was the basis of a letter to the editor criticizing the methodology and the resulting flawed conclusion.[11] Since this paper included all exposed patients, it is neither a cohort study not a clinical trial; it is simply a large case series of 20,000 patients from which we cannot draw a causal inference.

Studies With Comparison

If we therefore recognize the need for our study to include some type of comparison, what are the possible designs?

Historical Controls

We could use a comparison group from the past, called *historical controls.* Some refer to them as *external controls* or *synthetic controls*. We have a therapy today that we believe will be quite effective, and we would like to test it in a group of patients; we know that we need a comparison group. So, for comparison, we will go back to the records of patients with the same disease who were treated before the new therapy became available. This type of design seems inherently simple and attractive.

What are the problems in using historical controls? First, if today we decide to carry out the study just described, we may set up a very meticulous system for data collection from the patients currently being treated. But, of course, we cannot do that for the patients who were treated in the past, for whom we must abstract data from medical records which are likely useful for managing individual care but are fraught with error and omissions when used for research purposes. Consequently, if at the end of the study we find a difference in outcome between patients treated in the early period (historical controls) and patients treated in the later (current) period, we will not know whether there was a true difference in outcome or whether the observed difference was due only to a difference in the quality of the data collection. The data obtained from the study groups must be comparable in kind and quality; in studies using historical controls, this is often not the case.

The second problem is that if we observe a difference in outcome between the early group and the later group, we will not be sure that the difference is due to the therapy because many things other than the therapy change over calendar time (e.g., ancillary supportive therapy, living conditions, nutrition, and lifestyles). This is often referred to as "*secular changes*." Hence, if we observe a difference and if we have ruled out differences in data quality as the reason for the observed difference, we will not know whether the difference is a result of the drug we are studying or of other changes that take place in many other factors that may be associated with the outcome over calendar time. This is why when an investigator chooses historical controls, careful consideration should be made to whether there were major secular changes in accuracy of diagnosis, other treatments or management of the patient population being studied.

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However, at times, this type of design may be useful. For example, when a disease is uniformly fatal and a new drug becomes available, a decline in case-fatality that parallels use of the drug would strongly support the conclusion that the new drug is having an effect. Examples include the discovery of insulin to treat diabetes, of penicillin to treat serious infections, of streptomycin to treat tuberculosis, the St Jude protocol to treat children with acute lymphocytic leukemia and of tyrosine kinase inhibitors (TKIs) such as imatinib (Gleevec) to treat chronic myelocytic leukemia. The use of historical controls has also been used by regulatory authorities for approvals of new drugs. For example, pretomanid was developed by Tuberculosis (TB) Alliance as a combination drug (along with bedaquiline and linezolid) in the treatment of patients with highly drug-resistant forms of tuberculosis. During the clinical development program of the drug, FDA issued a Fast Track and Orphan Drug Designation given the rare disease status of the drug-resistant forms of TB, which potentially justifies the use of an external control arm. In 2019, pretomanid was approved by the FDA as a New Molecular Entity (NME) based on one single arm phase 3 trial.[12] However, while the trial itself was single arm, the sponsor (TB Alliance), used a Real-World Evidence (RWE) methodology to support the approval of the drug using the external control arm approach with the agreement of the FDA. They conducted a literature summary and case-matched analysis of historical control data for extensively resistant TB patients using carefully chosen inclusion and exclusion criteria. They were able to identify 16 research articles that met their criteria and calculated a pooled relative risk of a favorable outcome comparing the new combination therapy to the external control arm of 6.6 (95% confidence interval 4.6, 9.6, $P < .0001$).[13]

Simultaneous Nonrandomized Controls

Because of the importance of the problems posed by historical controls and the difficulties of dealing with changes over calendar time, an alternative approach is to use simultaneous controls that are not selected in a randomized manner. The problem with selecting simultaneous controls in a nonrandomized manner is illustrated by the following story:

> *A sea captain was given samples of anti-nausea pills to test during a voyage. The need for controls was carefully explained to him. Upon return of the ship, the captain reported the results enthusiastically. "Practically every one of the controls was ill, and not one of the subjects had any trouble. Really wonderful stuff." A skeptic asked how he had chosen the controls and the subjects. "Oh, I gave the stuff to my seamen and used the passengers as controls."*[14]

There are a number of possible approaches for selecting controls in such a nonrandomized fashion. One is to assign patients by the day of the month on which the patient is admitted to the hospital: for example, if admission is on an odd-numbered day of the month the patient is in group A, and if admission is on an even-numbered day of the month the patient is in group B. In a trial of anticoagulant therapy after World War II, in which this day-of-the-month method was used, it was discovered that more patients than expected were admitted on odd-numbered days. The investigators reported that "*as physicians observed the benefits of anticoagulant therapy, they speeded up, where feasible, the hospitalization of those patients ... who would routinely have been hospitalized on an even day in order to bring as many as possible under the odd-day deadline.*"[15]

The problem here is that the assignment system was predictable: it was possible for the physicians to know what the assignment of the next patient would be. The primary goal of randomization is to eliminate the possibility that the investigator will know what the assignment of the next patient will be, because such knowledge introduces the possibility of bias on the part of the investigator regarding the treatment group to which each participant will be assigned. Randomization, if done correctly, eliminates this type of selection bias.

Many years ago, a study was carried out of the effects of bacillus Calmette-Guérin (BCG) vaccination against tuberculosis in children from families with tuberculosis in New York City.[16] The physicians were told to divide the group of eligible children into a group to be immunized and a comparison or control group who were not immunized. As seen in Table 10.1, tuberculosis mortality was almost five times higher in the controls than in the vaccinated children. However, as the investigators wrote:

> *Subsequent experience has shown that by this method of selection, the tendency was to inoculate the children of the more intelligent and cooperative parents and to keep the children of the noncooperative parents as controls. This was probably of considerable error since the cooperative parent will not only keep more careful precautions, but will usually*

TABLE 10.1 Results of a Trial of Bacillus Calmette-Guérin Vaccination: I

		TUBERCULOSIS DEATHS	
	No. of Children	Number	%
Vaccinated	445	3	0.67
Controls	545	18	3.30

Data from Levine MI, Sackett MF. Results of BCG immunization in New York City. *Am Rev Tuberculosis.* 1946;53:517–532.

TABLE 10.2 Results of a Trial of Bacillus Calmette-Guérin Vaccination: II

		TUBERCULOSIS DEATHS	
	No. of Children	Number	%
Vaccinated	556	8	1.44
Controls	528	8	1.52

Data from Levine MI, Sackett MF. Results of BCG immunization in New York City. *Am Rev Tuberculosis.* 1946;53:517–532.

> *bring the child more regularly to the clinic for instruction as to child care and feeding.*[16]

Recognizing that the vaccinations were selectively performed in children from families that were more likely to be conscious of health and related issues, the investigators realized that it was possible that the case-fatality rate from tuberculosis was lower in the vaccinated group, not because of the vaccination itself but because these children were selected from more health-conscious families who had a lower risk of mortality from tuberculosis, with or without vaccination. To address this problem, a change was made in the study design: alternate children were vaccinated, and the remainder served as controls. This does not constitute randomization, but it was a marked improvement over the initial design. As seen in Table 10.2, there was now no difference between the groups.

ALLOCATING SUBJECTS USING RANDOMIZATION

In view of the problems discussed, randomization is the best approach in the design of a trial. Randomization means, in effect, tossing a coin to decide the assignment of a patient to a study group. The critical element of randomization is the unpredictability of the next assignment.[17]

How is randomization accomplished? Although random allocation (randomization) is currently usually done through computer generated programs, on occasion manual randomization is used either as a backup to computer-generation assignment or when access to a computer is limited. In this hypothetical example of manual assignment, we use a selection from a table of random numbers (Table 10.3). (Such random number tables are available in an appendix in most statistics textbooks or can be generated on computers.)

First, how do we look at Table 10.3? Note that the table is divided into 10 rows and 4 numbered columns (row numbers appear on the far left columns). The columns are numbered along the top, 00–04, 05–09, and so on. This means that the first number in column 00 is 5, the number in column 01 is 6, the number in column 03 is 3, etc. Similarly, the rows are numbered along the left, 00, 01, 02, and so on. Thus, it is possible to refer to any digit in the table by giving its column and row numbers. This is important if the quality of the randomization process is to be checked by an outsider. How do we use this table? Let us say that we are conducting a study in which there will be two groups: therapy A and therapy B. In this example, we will consider every odd number an assignment to A and every even number an assignment to B. We close our eyes and put a finger anywhere on the table and write down the column and row number that was our starting point. We also write down the direction we will move in the table from that starting

TABLE 10.3 Table of Random Numbers

	00–04	05–09	10–14	15–19
00	56348	01458	36236	07253
01	09372	27651	30103	37004
02	44782	54023	61355	71692
03	04383	90952	57204	57810
04	98190	89997	98839	76129
05	16263	35632	88105	59090
06	62032	90741	13468	02647
07	48457	78538	22759	12188
08	36782	06157	73084	48094
09	63302	55103	19703	74741

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point (horizontally to the right, horizontally to the left, up, or down). Let us assume that we point to the "5" at the intersection of column 07 and row 07 and move horizontally to the right. The first patient, then, is designated by an odd number, 5, and will receive therapy A. The second patient is also designated by an odd number, 3, and will receive therapy A. The third is designated by an even number, 8, and will receive therapy B, and so on. Note that the next patient assignment is not predictable; it is *not* a strict alternation, which would be predictable and hence subject to investigator bias, knowingly or unknowingly.

There are many ways of using a table of random numbers for allocating patients to treatment groups in a randomized trial (Box 10.1). Although many approaches are valid, the important point is to spell out *in writing* whatever approach is selected for use, before randomization is actually begun.

Having decided conceptually how to use the random numbers for allocating study participants, how do we make a practical decision as to which patients get which therapy? Let us assume, for example, that a decision has been made that odd digits will designate assignment to treatment A and even digits will designate treatment B. The treatment assignment that is designated by the random number is written on a card, and this card is placed inside an opaque envelope. Each envelope is labeled on the outside: Patient 1, Patient 2, Patient 3, and so on, to match the sequence in which the patients are enrolled in the study. For example, if the first random number is 2, a card for therapy B would be placed in the first envelope; if the next random number is 7, a card for therapy A in the second one, and so on, as determined by the random numbers.

BOX 10.1 Examples of Using A Random Numbers Table for Allocating Patients to Treatment Groups in A Randomized Trial

If we plan to compare two groups:

- We decide that even digits designate treatment A, odd digits designate treatment B, *or*
- We decide that digits 0–4 designate treatment A, digits 5–9 designate treatment B

If we plan to compare three groups:

- We decide that digits 1–3 designate treatment A, digits 4–6 designate treatment B, digits 7–9 designate treatment C, and digit 0 would be ignored

The envelopes are then sealed. When the first patient is enrolled, envelope 1 is opened and the assignment is read; this process is repeated for each of the remaining patients in the study.

However, this process is not foolproof. The following anecdote illustrates the need for careful quality control of any randomized study:

> *In a randomized study comparing radical and simple mastectomy for breast cancer, one of the surgeons participating was convinced that radical mastectomy was the treatment of choice and could not reconcile himself to performing simple mastectomy on any of his patients who were included in the study. When randomization was carried out for his patients and an envelope was opened that indicated simple mastectomy for the next assignment, he would set the envelope aside and keep opening envelopes until he reached one with an assignment to radical mastectomy.*

What is reflected here is the conflict experienced by many clinicians who enroll their own patients in randomized trials. On the one hand, the clinician has the obligation to do the best they can for the patient; on the other hand, when a clinician participates in a clinical trial, they are, in effect, asked to step aside from the usual decision-making role and essentially to "flip a coin" to decide which therapy the patient will receive. Thus, there is often an underlying conflict between the clinician's role and the role of the physician participating in enrolling patients in a clinical trial, and as a result, unintentional biases may occur.

This is such a common problem, particularly in large, multicenter trials, that randomization is not carried out by each participating clinical field center; rather, it is done by an impartial separate coordinating center. When a new patient is registered at a clinical center, the coordinating center is called, or an assignment is downloaded by the coordinating center. A randomized assignment is then made for that patient by the coordinating center, and the assignment is noted in both the clinical and coordinating centers.

What do we hope to accomplish by randomization? If we randomize properly, we achieve non-predictability of the next assignment; we do not have to worry that any subjective biases of the investigators, either overt or covert, may be introduced into the process of selecting patients for one treatment group or the other.

In addition, if the study is large enough and there are enough participants, we hope that randomization will increase the likelihood that the groups will be comparable to each other in regard to characteristics about which we may be concerned, such as sex, age, race, and severity of disease—all factors that may affect prognosis. Randomization is not a guarantee of comparability because chance may play a role in the process of random treatment assignment. However, if the treatment groups that are being randomized are large enough and the randomization procedure is free of bias, they will tend to be similar. In the meantime, if the two groups are found to be different according to some baseline variables, we can infer that these differences occurred by chance. (Note that even chance differences have to be adjusted for.)

Fig. 10.2 presents a hypothetical example of the effect of lack of comparability on a comparison of mortality rates of the groups being studied. Let us assume a study population of 2,000 subjects with myocardial infarctions, of whom half receive an intervention and the other half do not. Let us further assume that of the 2,000 patients, 700 have an arrhythmia and 1,300 do not. Case-fatality in patients with the arrhythmia is 50%, and in patients without the arrhythmia it is 10%.

Let us look at the nonrandomized study on the left side of Fig. 10.2. Because there is no randomization, the intervention groups may not be comparable in the proportion of patients who have the arrhythmia. Perhaps 200 in the intervention group may have the arrhythmia (with a case-fatality of 50%) and 500 in the no-intervention group may have the arrhythmia (with its 50% case-fatality). The

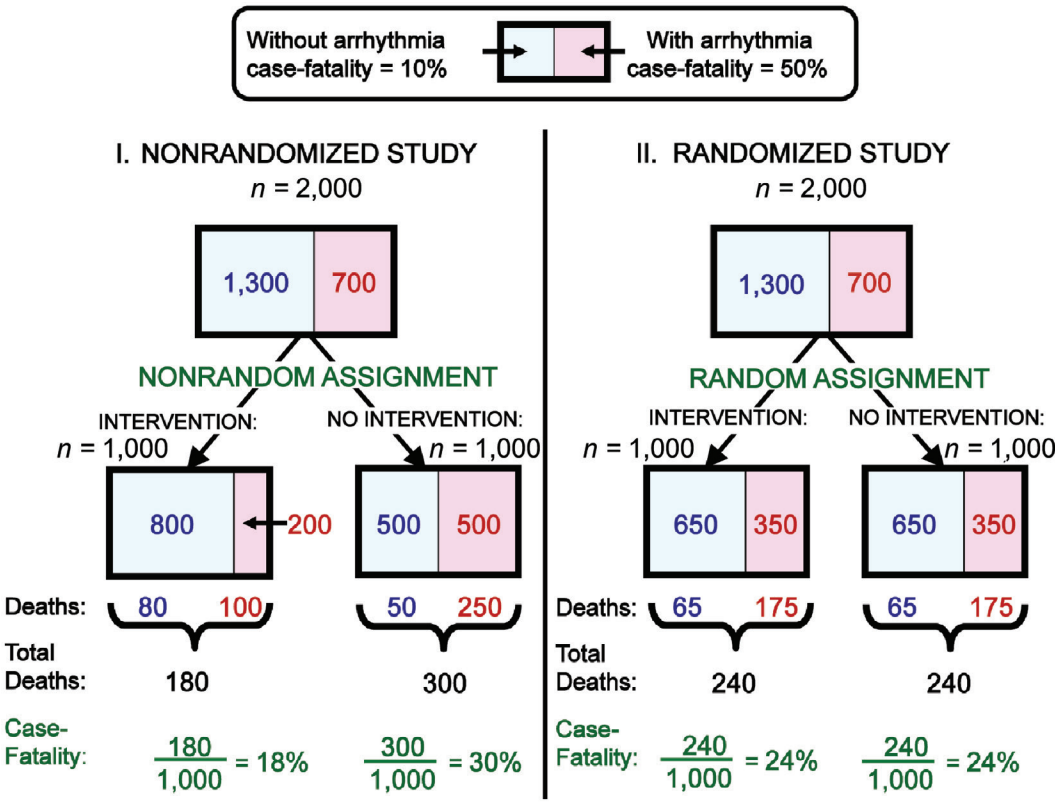

Fig. 10.2 Nonrandomized versus randomized studies. *I*, If the study is not randomized, the proportions of patients with arrhythmia in the two intervention groups may differ. In this example, individuals with arrhythmia are less likely to receive the intervention than individuals without arrhythmia. *II*, If the study is randomized, the proportions of patients with arrhythmia in the two intervention groups are more likely to be similar.

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resulting case-fatality will be 18% in the intervention group and 30% in the no-intervention group. We might be tempted to conclude that the intervention is more effective than not intervening.

However, let us now look at the randomized study on the right side of Fig. 10.2. As seen here, the groups are comparable, as is likely to occur when we randomize, so that 350 of the 1,000 patients in the intervention group and 350 of the 1,000 patients in the no-intervention group have the arrhythmia. When the case-fatality is calculated for this example, it is 24% in both groups. Thus the difference observed between intervention and no intervention when the groups were not comparable in terms of the arrhythmia was entirely due to the noncomparability and not to any effects of the intervention itself. In the nonrandomized study (also known as observational), arrhythmia is defined as a confounding variable (or confounder), as it is associated with case-fatality and is different between the groups. (Please note that although Fig. 10.2 shows 1,000 participants in both the intervention and no-intervention group, randomization does *not* guarantee an equal number of participants in each group; however, with large numbers, on average the two groups will generally be comparable.)

One might ask, if we are so concerned about the comparability of the groups, why not just match the groups on the specific variables about which we are concerned, rather than randomizing? The answer is that we can match only on variables that we know about and that we can measure. Thus, we cannot match on many variables that may affect prognosis, such as an individual's genetic constitution, elements of an individual's immune status, or other variables of which we may not even be aware and hence we will not measure during the study's data collection. In addition, if we match on a particular characteristic, we cannot analyze its association with the outcome because the two groups will already be identical regarding this characteristic.

To summarize, randomization increases the likelihood that the groups will be comparable not only in terms of variables that we recognize and can measure, but also in terms of variables that we may not recognize, may not be able to test now, and may not be able to measure with today's technologies. However, at the end of the day, randomization cannot always guarantee comparability of the groups being studied. We can analyze whether there are important differences between the two groups that may be associated with the trial outcome.

What Is the Main Purpose of Randomization?

The main purpose of randomization is to prevent any potential selection biases on the part of the investigators from influencing the assignment of participants to different treatment groups. When participants are randomly assigned to different treatment groups, all decisions on treatment assignment are removed from the control of the investigators. Thus, the use of randomization is crucial to protect the study from any biases that might be introduced consciously or subconsciously by the investigator into the assignment process.

As mentioned previously, although randomization often increases the comparability of the different treatment groups, randomization does not guarantee comparability. Another benefit of randomization is that to whatever extent it contributes to comparability, this contribution applies both to variables we can measure and to variables that we cannot measure and may not even be aware of, even though they may be important in interpreting the findings of the trial.

Stratified Randomization

Sometimes we may be particularly concerned about comparability of the groups in terms of one or a few important characteristics that we strongly think may influence prognosis or response to therapy in the groups being studied, but as we have just said, randomization does not ensure comparability. An option that can be used is *stratified randomization,* an assignment method that can be very helpful in increasing the likelihood of comparability of the study groups. In this section, we will show how this method is used to assign participants to different study groups.

For example, let us say that we are particularly concerned about age as a prognostic variable: prognosis is much worse in older patients than among the younger. Therefore, we are concerned that the two treatment groups be directly comparable in terms of age. Although one of the benefits of randomization is that it may increase the likelihood of such comparability, it does not guarantee it. It is still possible that after we randomize, we may, by chance, find that most of the older patients are in one group and most of the younger patients are in the other. Our results would then be impossible to interpret because the higher-risk patients would be clustered in one group and the lower-risk patients in the other. Any difference in outcome between intervention groups may then be attributable to this difference in the

age distributions of the two groups rather than to the effects of the intervention.

In *stratified randomization,* we first stratify (stratum = layer or level) our study population by each variable that we consider important and then randomize participants to treatment groups within each stratum.

Let us consider the example shown in Fig. 10.3. We are studying 1,000 patients and are concerned that sex and age are important determinants of prognosis. If we randomize, we do not know what the composition of the groups may be in terms of sex and age; therefore, we decide to use stratified randomization.

We first stratify the 1,000 patients by sex into 600 males and 400 females. We then separately stratify the males by age and the females by age. We now have four groups (strata): younger males, older males, younger females, and older females. We now randomize *within each group (stratum),* and the result is a new treatment group and a current treatment group for each of the four groups. As in randomization without stratification, we end up with two intervention groups, but having initially stratified the groups, we increase the likelihood that the two groups will be comparable in terms of sex and age. (As in Fig. 10.2, Fig. 10.3 shows that randomization results in an equal number of participants in each treatment group, although this result is *not* guaranteed by randomization.) We may also decide to examine the results in each stratum, e.g., compare the randomized groups in younger women (say under 50 years old) and older women, with the same analysis done for men. Subgroup analysis according to randomization strata is akin to small, randomized trials, which may not be sufficiently statistically powered as the overall trial to detect treatment differences,

DATA COLLECTION ON SUBJECTS

As mentioned earlier, it is essential that the data collected for each of the study groups be of the same quality. We do not want any differences in results between the groups to be due to differences in the quality or completeness of the data that were collected in the study groups. Let us consider some of the variables about which data need to be obtained on the subjects.

Treatment (Assigned and Received)

What data are needed? First, we must know to which treatment group the patient was assigned. In addition, we must know which therapy the patient *actually* received. It is important to know, for example, if the patient was assigned to receive treatment A but did not comply. A patient may agree to be randomized but may later change his or her mind and refuse to comply. Conversely, it is also clearly important to know whether a patient who was not assigned to receive treatment A may have taken treatment A on his or her own, often without the investigators knowing. This can also happen if the investigator or the clinical

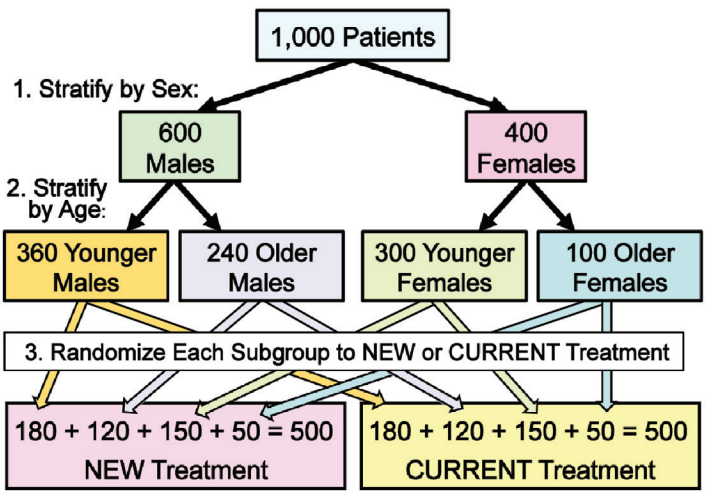

Fig. 10.3 Example of stratified randomization. See discussion in text.

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research coordinator inadvertently administers the wrong treatment (or wrong dose) to the patient.

Outcome

The need for comparable measurements in all study groups is particularly true for measurements of outcome. Such measurements include both improvement (the desired effect) and any side effects (often referred to as adverse events) that may appear. There is therefore a need for explicitly stated criteria for all outcomes to be measured in a study. Once the criteria are explicitly stated, we must be certain that they are measured comparably in all study groups. In particular, the potential pitfall of outcomes being measured more carefully in those receiving a new drug than in those receiving currently available therapy must be avoided. Masking (blinding), discussed later, can prevent much of this problem, but because masking is not always possible, attention must be given to ensuring comparability of measurements and of data quality in all of the study groups.

All-Cause Mortality Outcome ("Public Health Outcome")

On occasion a medication or a preventive strategy for mortality that is effective with regard to the main outcome of interest does not increase event-free survival. For example, in the 13-year follow-up of the European Randomized Study of Screening for Prostate Cancer, there was a reduction of approximately 27% in prostate cancer mortality.[18] However, overall mortality (also known as "public health outcome") was similar in the two study groups, thus suggesting that effectiveness of screening with regard to all-cause mortality was null.

Prognostic Profile at Entry

If we know the risk factors for a bad outcome, we want to verify that randomization has provided reasonable similarity between the two groups in terms of these risk factors. For example, if age is a significant risk factor, we would want to know that randomization has resulted in groups that are comparable for age. Data for prognostic factors should be obtained at the time of subject entry into the study, and then the two (or more) groups can be compared on these factors at baseline (i.e., before the treatment is provided). Another strategy to evaluate comparability is to examine an outcome totally unrelated to the treatment that is being evaluated. For example, if the randomized trial's objective is to evaluate a new medication for migraines, it is expected that mortality from cancer would be similar in the two groups.

Masking (Blinding)

Masking involves several components: First, we would like the subjects not to know which group they are assigned to. This is of particular importance when the outcome is a subjective measure, such as a psychiatric condition, self-reported severity of headache or low back pain. If the patient knows that they are receiving a new therapy, enthusiasm and certain psychological factors on the part of the patient may operate to elicit a positive response even if the therapy itself had no positive biologic or clinical effect.

How can subjects be masked? One way is by using a *placebo*, an inert substance that looks, tastes, and smells like the active agent. However, use of a placebo does not automatically guarantee that the patients are masked (blinded). Some participants may try to determine whether they are taking the placebo or active drug. For example, in a randomized trial of vitamin C for the common cold, patients were blinded by use of a placebo and were then asked whether they knew or suspected which drug they were taking. Even with masking of medications, participants may decide to alternate doses with another participant so that they hope they each get some of the study medication; this was commonly seen when new antiretroviral therapy was initiated for AIDS in resource limited settings.

As seen in Table 10.4, of the 52 people who were receiving vitamin C and were willing to make a guess, 40 stated they had been receiving vitamin C. Of the 50 who were receiving placebo, 39 said they were receiving placebo. How did they know? They had bitten into the capsule and could tell by the bitter taste. Does it make any difference that they knew? The data suggest that the rate of colds was higher in subjects who received vitamin C but thought they were receiving placebo than in subjects who received placebo but thought they were receiving vitamin C. Thus, we must be very concerned about lack of masking of the subjects and its potential effects on the results of the study, particularly when we are dealing with subjective end points.

Use of a placebo is also important for studying the rates of side effects and reactions, formally called *adverse events*. The Physicians' Health Study was a randomized

TABLE 10.4 Randomized Trial of Vitamin C and Placebo for the Common Cold: Results of a Questionnaire Study to Determine Whether Subjects Suspected Which Agent They Had Been Given

	SUSPECTED DRUG		
Actual Drug	**Vitamin C**	**Placebo**	**Total**
Vitamin C	40	12	52
Placebo	11	39	50
Total	51	51	102

$P < .001$.

From Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold. A prophylactic and therapeutic trial. *JAMA*. 1975;231:1038. Copyright 1975, American Medical Association.

TABLE 10.5 Physicians' Health Study: Side Effects According to Treatment Group

Side Effect	Aspirin Group (%)	Placebo Group (%)	*P*
GI symptoms (except ulcer)	34.8	34.2	.48
Upper GI tract ulcers	1.5	1.3	.08
Bleeding problems	27.0	20.4	<.00001

GI, Gastrointestinal.

Data from Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the Ongoing Physicians' Health Study. *N Engl J Med.* 1989;321:129–135. Copyright 1989, Massachusetts Medical Society. All rights reserved.

trial of the use of aspirin to prevent myocardial infarctions. Table 10.5 shows the side effects that were reported in groups receiving aspirin and those receiving placebo in this study.

Note the high rates of reported reactions in people receiving placebo. Thus it is not sufficient to say that 34% of the people receiving aspirin had gastrointestinal symptoms; what we really want to know is the extent to which the risk of side effects is increased in people taking aspirin compared with those not taking aspirin (i.e., those taking placebo). Thus, the placebo plays a major role in identifying both the real benefits of an agent and its side effects. Sometimes it is possible to use a medication in both the new therapy and in the placebo groups to prevent the occurrence of the most obvious side effects of the therapy. In the aspirin example, a proton pump inhibitor, which is a class of medication that is used to prevent gastrointestinal symptoms from excess acid, could be given to both randomized groups, thus masking the participants with regard to the group to which they were allocated. In addition to masking (or blinding) the subjects, we also want to mask the observers or data collectors in regard to which group a patient is in. The masking of both participants and study personnel is called "double masking." Some years ago, a study was being conducted to evaluate coronary care units in the treatment of myocardial infarction. It was planned in the following manner:

> *Patients who met strict criteria for categories of myocardial infarction [were to] be randomly assigned either to the group that was admitted immediately to the coronary care unit or to the group that was returned to their homes for domiciliary care. When the preliminary data were presented, it was apparent in the early phases of the experiment that the group of patients labeled as having been admitted to the coronary care unit did somewhat better than the patients sent home. An enthusiast for coronary care units was uncompromising in his insistence that the experiment was unethical and should be terminated and that the data showed that all such patients should be admitted to the coronary care unit. The statistician then revealed the headings of the data columns had been interchanged and that really the home care group seemed to have a slight advantage. The enthusiast then changed his mind but could not be persuaded to declare coronary care units unethical.*[19]

The message of this example is that each of us comes to whatever study we are conducting with a certain number of subconscious or conscious biases and preconceptions. The methods discussed in this chapter and Chapter 11 are designed to shield the study from the biases of the investigators.

We will now turn to two other aspects of the design of randomized trials: crossover and factorial designs.

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CROSSOVER

Another important issue in clinical trials is *crossover.* Crossover may be of two types: planned or unplanned.

A *planned crossover* is shown in Fig. 10.4. In this example, a new treatment is being compared with current treatment. Subjects are randomized to new treatment or current treatment (see Fig. 10.4A). After being observed for a certain period of time on one therapy and after any changes are measured (see Fig. 10.4B), the patients are switched to the other therapy (see Fig. 10.4C). Both groups are then again observed for a certain period of

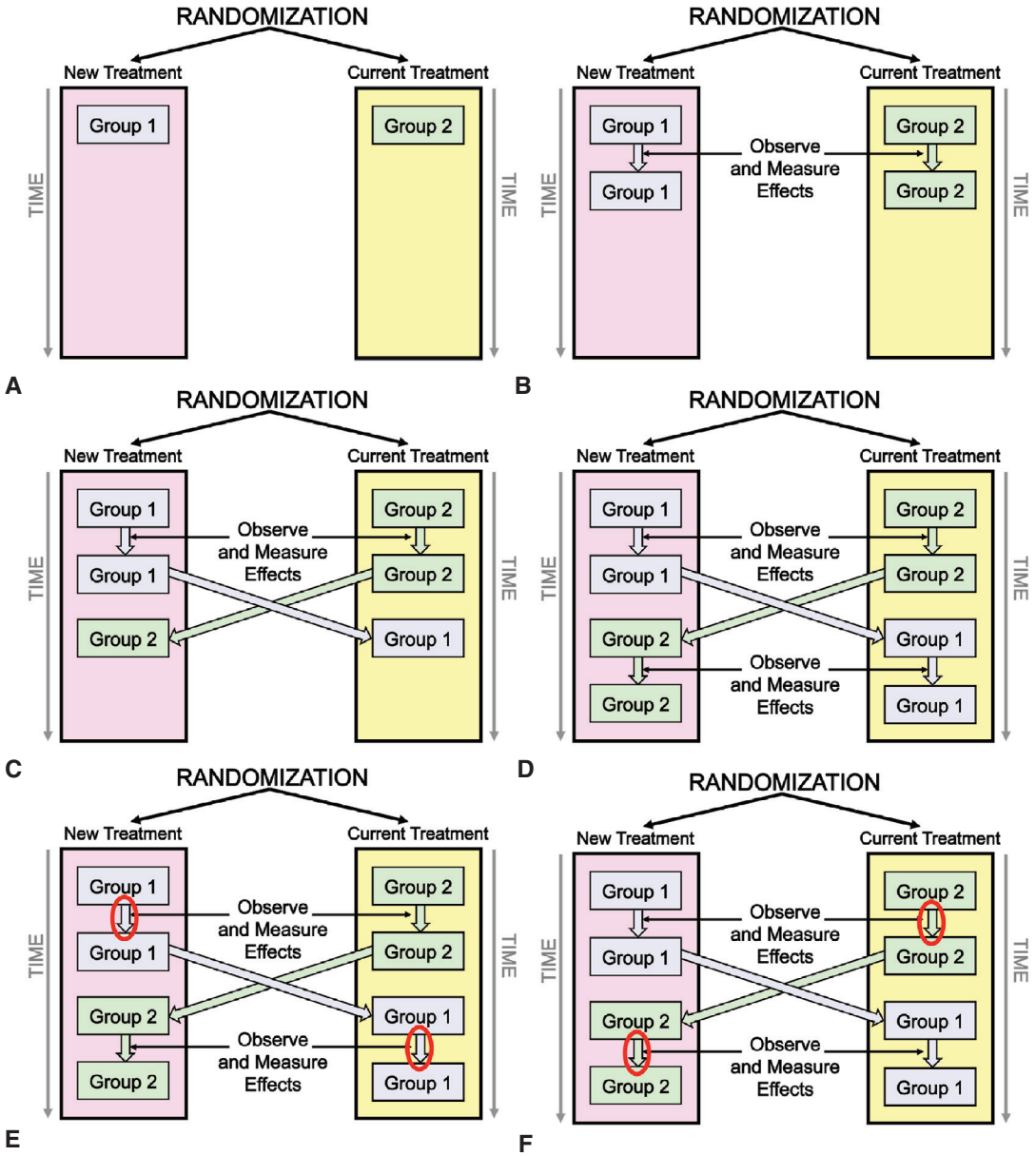

Fig. 10.4 (A–F) Design of a **planned crossover** trial. See discussion in text.

time (see Fig. 10.4D). Changes in group 1 patients while they are on the new treatment can be compared with changes in these patients while they are on the current treatment (see Fig. 10.4E). Changes in group 2 patients while they are on the new treatment can also be compared with changes in these patients while they are on the current treatment (see Fig. 10.4F). Thus each patient can serve as his or her own control, holding constant the variation between individuals in many characteristics that do not vary over time and that could potentially affect a comparison of the efficacy of the two agents in the trial.

This type of design is very attractive and useful provided that certain cautions are taken into account. First is that of *carryover:* For example, if a subject is changed from therapy A to therapy B and observed under each therapy, the observations under therapy B will be valid only if there is no residual carryover from therapy A. There must be enough of a "washout period" to be sure none of therapy A, or its effects, remains before starting therapy B. Second, the order in which the therapies are given may elicit psychological responses. Patients may react differently to the first therapy given in a study as a result of the enthusiasm that is often accorded a new study (*Hawthorne effect*); this enthusiasm may diminish over time. We therefore want to be sure that any differences observed are indeed due to the agents being evaluated, and not to any effect of the order in which they were administered. Finally, the planned crossover design is clearly not possible if the new therapy is surgical or if the new therapy cures the disease.

A more important consideration is that of an *unplanned crossover.* This is also called *contamination of treatment arms.* Fig. 10.5A shows the design of a randomized trial of coronary bypass surgery, comparing it with medical care for coronary heart disease. Randomization is carried out after informed consent has been obtained. Although the initial design is straightforward, in reality, unplanned crossovers may occur. Some subjects randomized to bypass surgery may begin to have second thoughts and decide not to have the surgery (see Fig. 10.5B). They are therefore crossovers into the medical care group (see Fig. 10.5C). In addition, the condition of some subjects assigned to medical care may begin to deteriorate and urgent bypass surgery may be required (see Fig. 10.5B)—these subjects are crossovers from the medical to the surgical care group (see Fig. 10.5C). The patients seen on the left in Fig. 10.5D are now treated surgically, and those on the right in this figure are treated medically. Those treated surgically include some who were randomized to surgery (shown in pink) and some who crossed over to surgery (shown in yellow). Those treated medically include some who were randomized to medical treatment (shown in yellow) and some who crossed over to medical treatment (shown in pink).

Unplanned crossovers pose a serious challenge in analyzing the data. If we analyze according to the original assignment (called an *intention to treat analysis*), we will include in the surgical group some patients who received only medical care, and we will include in the medical group some patients who had surgery. In other words, we would compare the patients according to the treatment to which they were originally randomized, regardless of what treatment actually occurred. Fig. 10.5E shows an *intention to treat* analysis in which we compare the group in pink (randomized to surgical treatment) with the group in yellow (randomized to medical treatment). Although it may be counterintuitive, it is the most conservative analysis of randomized trials, and also highly regarded by regulatory authorities for the purpose of new drug approvals. If, however, we analyze according to the treatment that the patients actually receive *(as treated analysis)*, we will have broken, and therefore lost the benefits of, the randomization. In essence, *as treated* analysis of a randomized trial can be considered as an analysis of a cohort study since randomization is not intact anymore and, thus, observational (nonrandomized) study biases may have occurred.

No perfect solution is available for this dilemma. Current practice is to perform the primary analysis by *intention to treat*—according to the original randomized assignment. We would hope that the results of other comparisons would be consistent with this primary approach. The bottom line is that because there are no perfect solutions, the number of unplanned crossovers must be kept to a minimum. Obviously, if we analyze according to the original randomization and there have been many crossovers, the interpretation of the study results will be questionable. If the number of crossovers becomes large, the problem of interpreting the study results may become insurmountable.

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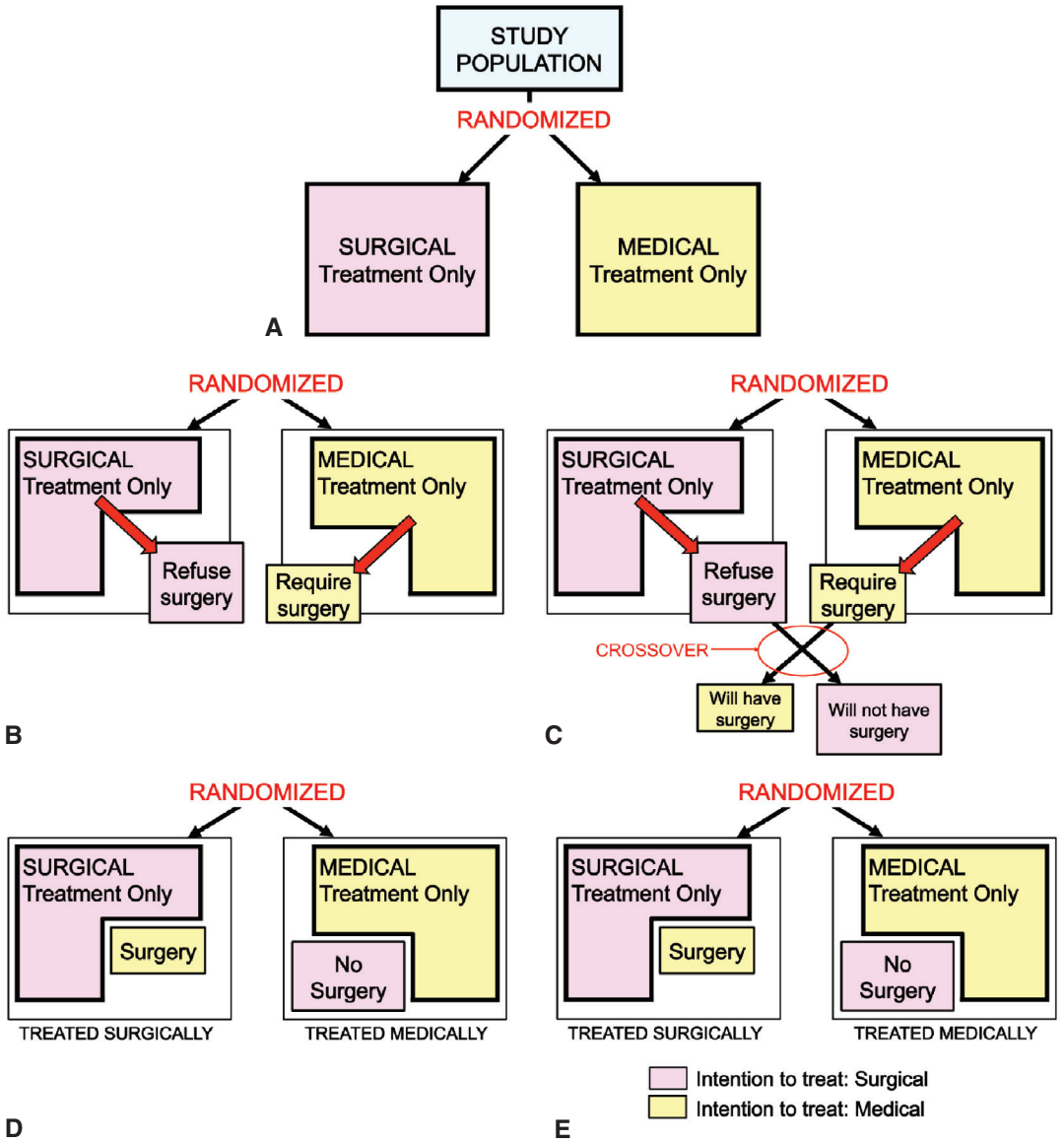

Fig. 10.5 **(A–E) Unplanned crossover** in a study of cardiac bypass surgery and the use of intention to treat analysis. **(A)** Original study design. **(B–D)** Unplanned crossovers. **(E)** Use of intention to treat analysis.

FACTORIAL DESIGN

An attractive alternative option in the study designs discussed in these chapters is the *factorial design*. Assuming that two drugs are to be tested, the anticipated outcomes for the two drugs are different, and their modes of action are independent, one can economically use the same study population for testing both drugs. This factorial type of design is shown in Fig. 10.6.

If the effects of the two treatments are indeed completely independent, we could evaluate the effects of treatment A by comparing the results in cells $a + c$ to the results in cells $b + d$ (Fig. 10.7A). Similarly, the results for treatment B could be evaluated by comparing the effects

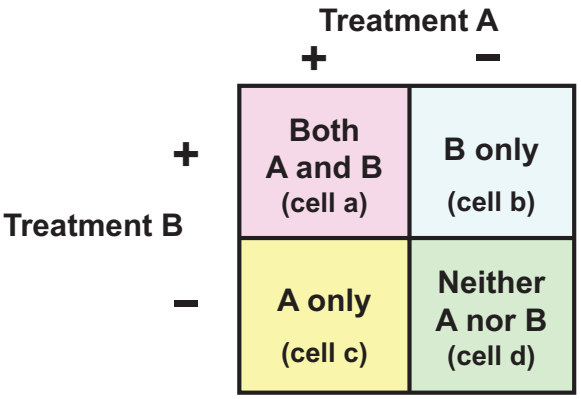

Fig. 10.6 Factorial design for studying the effects of two treatments.

in cells $a + b$ to those in cells $c + d$ (see Fig. 10.7B). In the event that it is decided to terminate the study of treatment A, this design permits continuing the study to determine the effects of treatment B.

An example of a factorial design is seen in the Physicians' Health Study.[20] More than 22,000 physicians were randomized using a 2 × 2 factorial design that tested aspirin for primary prevention of cardiovascular disease and beta carotene for primary prevention of cancer. Each physician received one of four possible interventions: both aspirin and beta carotene, neither aspirin nor beta carotene, aspirin and beta carotene placebo, or beta carotene and aspirin placebo. The resulting four groups are shown in Figs. 10.8 and 10.9. The aspirin part of the study (Fig. 10.10A) was terminated early, on the advice

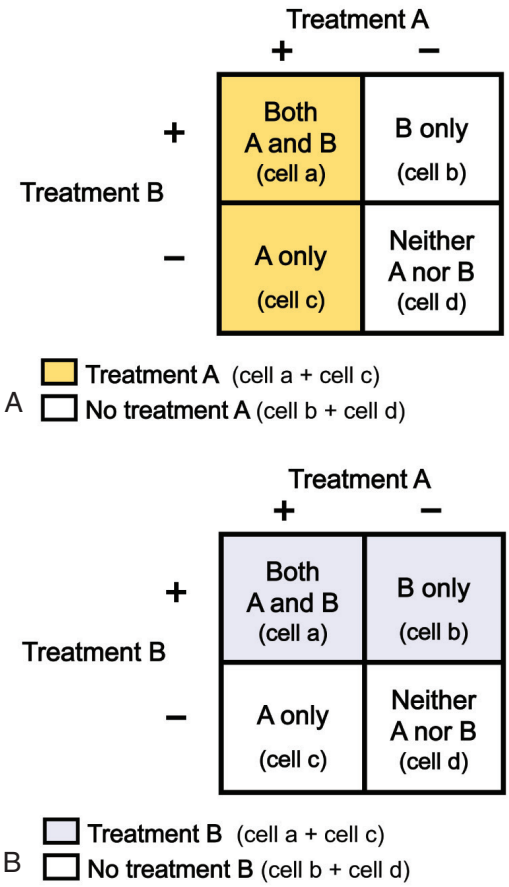

Fig. 10.7 (A and B) Factorial design. **(A)** The effects of treatment A (*orange cells*) versus no treatment A. **(B)** The effects of treatment B (*purple cells*) versus no treatment B.

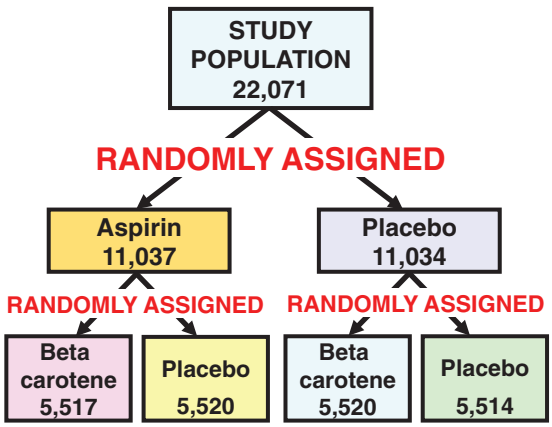

Fig. 10.8 Factorial design used in a study of aspirin and beta carotene.

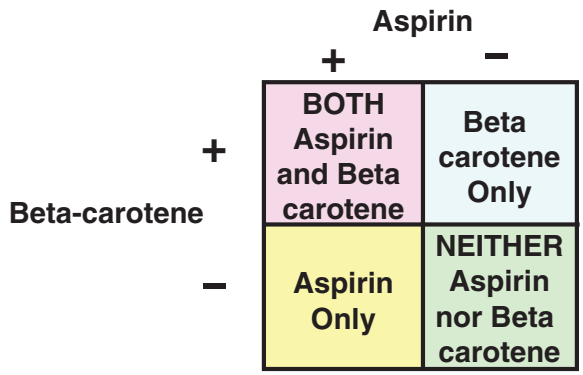

Fig. 10.9 Factorial design of the study of aspirin and beta carotene in 2 × 2 table format.

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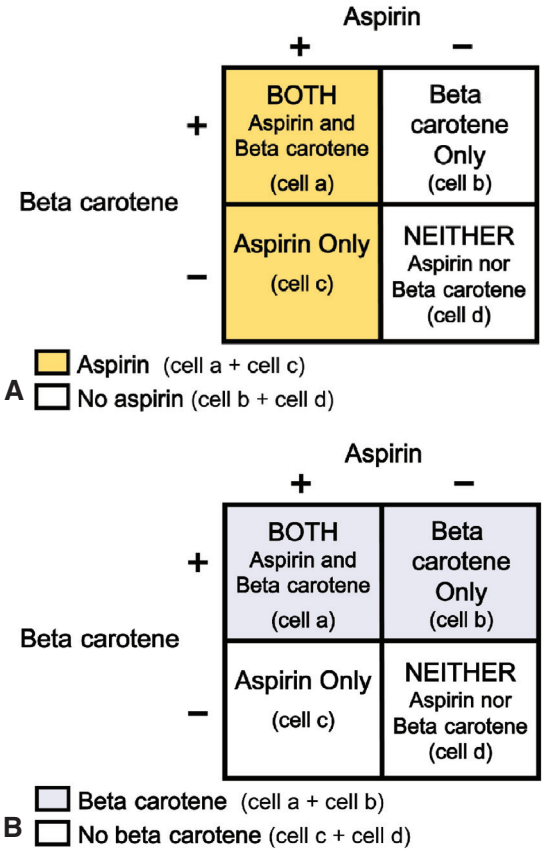

Fig. 10.10 (A and B) Factorial design. **(A)** The effects of aspirin (*orange cells*) versus no aspirin. **(B)** The effects of beta carotene (*purple cells*) versus no beta carotene.

of the external data monitoring board, because a statistically significant 44% decrease in the risk of first myocardial infarction was observed in the group taking aspirin. The randomized beta carotene component (see Fig. 10.01B) continued until the originally scheduled date of completion. After 12 years of beta carotene supplementation, no benefit or harm was observed in terms of the incidence of cancer or heart disease or death from all causes. Subsequent reports have shown greater risk of cancer with beta carotene in smokers.[21]

NONCOMPLIANCE

Patients may agree to be randomized, but following randomization they may not comply with the assigned treatment. Noncompliance may be overt or covert: On the one hand, people may overtly articulate their refusal to comply or may stop participating in the study. These noncompliers are also called *dropouts* from the study. On the other hand, people may just stop taking the agent assigned without admitting this to the investigator or the study staff. Whenever possible, checks on potential noncompliance are built into the study. These may include, for example, urine or blood tests for the agent being tested or for one of its metabolites.

Another problem in randomized trials has been called *drop-ins*. Patients in one group may inadvertently take the agent assigned to the other group. For example, in a trial of the effect of aspirin for prevention of myocardial infarction, patients were randomized to aspirin or to no aspirin. However, a problem arose in that, because of the large number of over-the-counter preparations that contain aspirin, many of the control patients might well be taking aspirin without knowing it. This was previously discussed as an unplanned crossover. Two steps were taken to address this problem: (1) controls were provided with lists of aspirin-containing over-the-counter preparations that they should avoid, and (2) urine tests for salicylates were carried out both in the aspirin group and in the controls.

The net effect of noncompliance on the study results will be to reduce any observed differences (i.e., driving the difference toward the null) because the treatment group will include some who did not receive the therapy, and the no-treatment group may include some who received the treatment. Thus, the groups will be less different in terms of therapy than they would have been had there been no noncompliance, so that even if there is a difference in the effects of the treatments, it will appear much smaller.

One approach that was used in the Veterans Administration Study of the Treatment of Hypertension[22] was to carry out a pilot study in which compliers and noncompliers were identified. When the actual full study was later carried out, the study population was limited to those who had been compliers during the pilot study (sometimes referred to as a "run-in period"). The problem with this approach is that when we want to generalize from the results of such a study, we can only do so to other populations of compliers, which may be different from the population in any free-living community, which would consist of both compliers and noncompliers.

Table 10.6 shows data from the Coronary Drug Project reported by Canner and coworkers.[23] This study was a comparison of clofibrate and placebo for lowering cholesterol. The table presents the mortality in the two groups.

TABLE 10.6 Coronary Drug Project: 5-Year Mortality in Patients Given Clofibrate or Placebo

	No. of Patients	Mortality (%)
Clofibrate	1,065	18.2
Placebo	2,695	19.4

Modified from Canner PL, Forman SA, Prud'homme GJ, for the Coronary Drug Project Research Group. Influence of adherence to treatment and response to cholesterol on mortality in the coronary drug project. *N Engl J Med.* 1980;303:1038–1041.

TABLE 10.7 Coronary Drug Project: 5-Year Mortality in Patients Given Clofibrate or Placebo According to Level of Compliance

	No. of Patients	Mortality (%)
Clofibrate		
Poor complier (<80%)	357	24.6
Good complier (≥80%)	708	15.0
Placebo	2,695	19.4

Modified from Canner PL, Forman SA, Prud'homme GJ, for the Coronary Drug Project Research Group. Influence of adherence to treatment and response to cholesterol on mortality in the coronary drug project. *N Engl J Med.* 1980;303:1038–1041.

No large difference in 5-year mortality was seen between the two groups. The investigators speculated that perhaps this was the result of the patients not having taken their medication. Table 10.7 shows the results of separating the clofibrate subjects into good compliers and poor compliers. Here we see the 5-year mortality was 24.6% in the poor-complier group compared with 15% in the good-complier group. We might thus be tempted to conclude that compliance was indeed the factor that produced the results seen in Table 10.6: no significant difference between the clofibrate and placebo groups.

Table 10.8 separates both groups, clofibrate and placebo, into compliers and noncompliers. Even in the placebo group, 5-year mortality in the poor compliers was higher than in the good compliers: 28% compared with 15%. One way to maximize compliance is to administer a single pill that includes a combination of two medications needed to achieve a therapeutic target. This is commonly called fixed-dose combinations (FDCs). A systematic review and meta-analysis found that the use of

TABLE 10.8 Coronary Drug Project: 5-Year Mortality in Patients Given Clofibrate or Placebo According to Level of Compliance

	CLOFIBRATE		PLACEBO	
Compliance	No. of Patients	Mortality (%)	No. of Patients	Mortality (%)
Poor (<80%)	357	24.6	882	28.2
Good (≥80%)	708	15.0	1,813	15.1
Total Group	1,065	18.2	2,695	19.4

Modified from Canner PL, Forman SA, Prud'homme GJ, for the Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. *N Engl J Med.* 1980;303:1038–1041.

FDCs of antihypertensive medications is associated with a significant improvement in medication compliance or persistence, despite non-statistically significant yet beneficial trends in blood pressure and adverse effects.[24]

What can we learn from these tables? People who do not comply or who do not participate in studies differ from those who do comply and who do participate. Therefore, in conducting a study to evaluate a therapy or other intervention, we cannot offer the agent to a population and compare the effects in those who take the agent to the effects in those who refuse or do not, because the two groups are basically different in terms of many demographic, social, psychological, and cultural variables that may have important roles in determining outcome. These are all forms of *selection bias* that were discussed previously when we talked about observational study designs. Randomization, or some other approach that reduces selection bias, is essential in a valid clinical trial.

CONCLUSION

The randomized trial is generally considered the gold standard of study designs. For the purpose of new drug approval by regulatory authorities, results of the randomized, double-masked, placebo-controlled clinical trial are considered the highest level of evidence. When hierarchies of study design are created to assess the strength of the available evidence supporting clinical and public health policy, randomized trials are virtually always at the top of the list when study designs are ranked in order of descending quality. However, a recently

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developed observational study approach—Mendelian randomization—the discussion of which is not within the scope of this textbook, mimics random allocation if its rather stringent assumptions can be met.[25]

This chapter has discussed many of the components of the randomized trial that are designed to shield the study from any preconceptions and biases of the investigator and of others involved in conducting the study, as well as from other biases that might inadvertently be introduced. In Chapter 11 we will address some other issues relating to the design of randomized trials and will consider several interesting examples and applications of the randomized trial design. Later in this book, we will discuss the use of randomized trials and other study designs for evaluating health services and for studying the effectiveness of screening.

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REVIEW QUESTIONS FOR CHAPTERS 10 AND 11 ARE AT THE END OF CHAPTER 11.

11

Randomized Trials: Some Further Issues

LEARNING OBJECTIVES

- To define key concepts of epidemiologic study design in the context of randomized trials: sample size, type I error, type II error, power, generalizability (external validity), and internal validity.
- To calculate and interpret efficacy in a randomized trial.
- To describe the design and results of five historically important randomized trials.
- To define the four major phases of randomized trials that are used by the US Food and Drug Administration for evaluating new drugs in the United States.
- To introduce several ethical considerations as they relate to randomized trials.
- To discuss the rationale for requiring the registration of new randomized trials in advance of their launch.

SAMPLE SIZE

At a scientific meeting some years ago, an investigator presented the results of a study he had conducted to evaluate a new drug in sheep. "After taking the drug," he reported, "one-third of the sheep were markedly improved, one-third of the sheep showed no change, and the other one ran away."

This story introduces one of the most frequent questions asked by physicians conducting trials of new agents, or for that matter by anyone conducting evaluative studies: "How many subjects do we have to study?" The time to answer this question is *before* the study is done. All too often studies are conducted, large amounts of money and other resources are invested, and only after the study has been completed do the investigators find that from the beginning, they had too few subjects to obtain meaningful results.

The question of how many subjects are needed for study is not based on mystique. This section presents the logic of how to approach the question of sample size. Let's begin this discussion of sample size with Fig. 11.1.

We have two jars of beads, each containing 100 beads, some white and some blue. The jars are opaque ("masked"), so (despite their appearance in the figure) we cannot see the colors of the beads in the jars just by looking at the jars. We want to know whether the distribution of the beads by color differs in jars A and B. In other words, is there a larger (or smaller) proportion of blue beads in jar A than in jar B?

To answer this question, let's take a sample of 10 beads from jar A in one hand and a sample of 10 beads from jar B in the other. On the basis of the color distribution of the 10 beads in each hand, we will try to reach a conclusion about the color distribution of all 100 beads in each of the jars.

Let's assume that (as shown in Fig. 11.2) in one hand we have nine blue beads and one white bead from jar A, and in the other hand we have two blue beads and eight white beads from jar B. Can we conclude that 90% of the beads in jar A are blue and that 10% are white? Clearly, we cannot. It is possible, for example, that of the 100 beads in jar A, 90 are white and 10 are blue, but *by chance* our 10-bead sample includes 9 blue and 1 white. This is possible but highly unlikely. Similarly, in regard to jar B,

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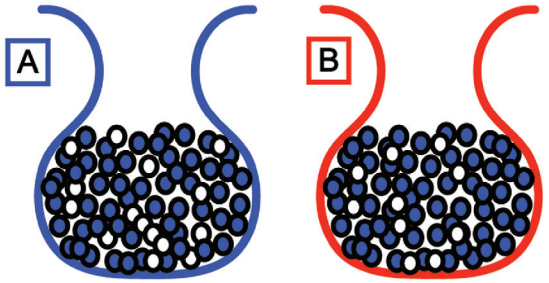

Fig. 11.1 (A) and (B) Two opaque jars, each holding 100 beads, some blue and some white.

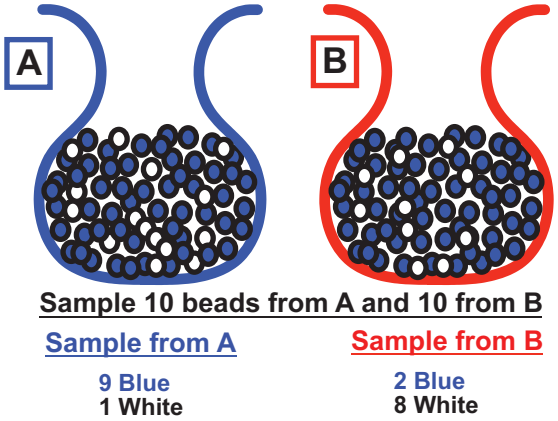

Fig. 11.2 Samples of 10 beads from jar A and 10 beads from jar B.

we cannot conclude that 20% of the beads are blue and 80% are white. It is conceivable that 90 of the 100 beads are blue and 10 are white, but that *by chance* the 10-bead sample includes 2 blue beads and 8 white beads. This is conceivable but, again, highly unlikely.

On the basis of the distributions of the 10-bead samples in each hand, could we say that the distributions of the 100 beads in the two jars are different? Given the samples in each hand, could it be, for example, that the distribution of beads in each jar is 50 blue and 50 white? Again, it is possible, but it is not likely. We cannot exclude this possibility on the basis of our samples. We are looking at samples and trying to draw a conclusion regarding a whole population—the jars from which we have drawn the samples.

Let's consider a second example, shown in Fig. 11.3. Again, we draw two samples. This time, the 10-bead sample from jar A consists of 7 blue beads and 3 white beads, and the 10-bead sample from jar B also consists

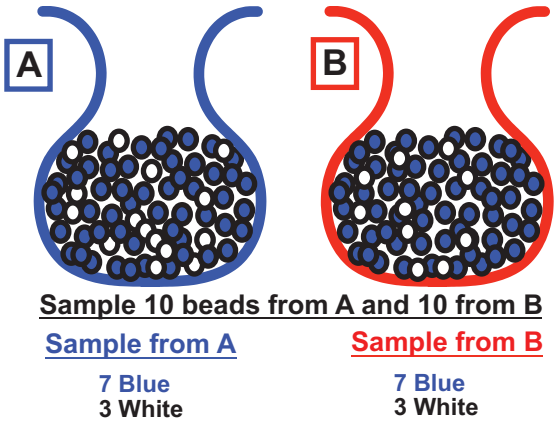

Fig. 11.3 Samples of 10 beads from jar A and 10 beads from jar B.

of 7 blue beads and 3 white beads. Could the color distribution of the beads in the two jars be the same? Clearly, it could. Could we have drawn these two samples of 7 blue beads and 3 white beads from both jars if the distribution is actually 90 white beads and 10 blue beads in jar A and 90 blue beads and 10 white beads in jar B? Yes, possibly, but unlikely.

When we carry out a study, we are only looking at the sample of subjects in our study, such as a sample of patients with a certain illness who are being treated with treatment A or with treatment B. From the study results we want to draw a conclusion that goes beyond the study population—is treatment A more effective than treatment B in the total universe of all patients with this disease who might be treated with treatment A or treatment B? The same issue that arose with the 10-bead samples arises when we want to derive a conclusion regarding all patients from the sample of patients included in our study. Rarely, if ever, is a study conducted in all patients with a disease or in all patients who might be treated with the drugs in question.

Given this background, let's now consider a trial in which groups receiving one of two therapies, therapy A and therapy B, are being compared. (Keep in mind the sampling of beads just discussed.) Before beginning our study, we can list the four possible study outcomes (Box 11.1):

1. It is possible that in reality there is no difference in efficacy between therapy A and therapy B. In other words, therapy A is no better and no worse than therapy B. When we do our study, we correctly

Box 11.1 Four Possible Conclusions When Testing Whether or NOT the Treatments Differ

- **When, in reality, the treatments do** not **differ:**
  1. We may correctly conclude that they do not differ,
     or
  2. In error, we may conclude that they do differ.
- **When, in reality, the treatments** do **differ:**
  3. In error, we may conclude that they do not differ,
     or
  4. We may correctly conclude that they do differ.

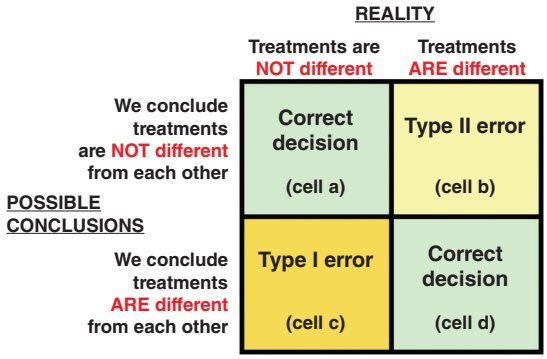

Fig. 11.4 Possible outcomes of a randomized trial: type I and type II errors.

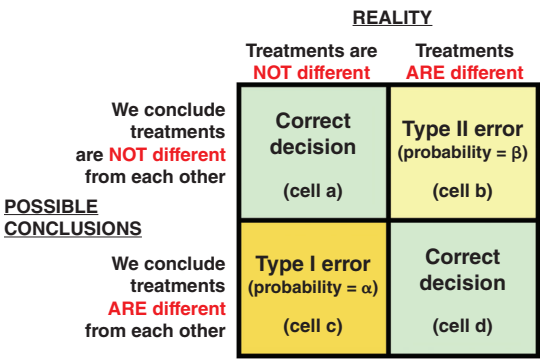

Fig. 11.5 Possible outcomes of a randomized trial: α and β.

conclude on the basis of our samples that the two groups do not differ.

2. It is possible that in reality there is no difference in efficacy between therapy A and therapy B, but in our study we found a difference between the groups and therefore concluded, on the basis of our samples, that there is a difference between the therapies. This conclusion, based on our samples, is in error.
3. It is possible that in reality there is a difference in efficacy between therapy A and therapy B, but when we examine the groups in our study, we find no difference between them. We therefore conclude, on the basis of our samples, that there is no difference between therapy A and therapy B. This conclusion is in error.
4. It is possible that in reality there is a difference in efficacy between therapy A and therapy B, and when we examine the groups in our study, we find that they differ. On the basis of these samples, we correctly conclude that therapy A differs from therapy B.

These four possibilities constitute all of the possible outcomes after we complete our study. Let's look at these four possibilities as presented in a 2 × 2 table (Fig. 11.4). Two columns represent reality—either therapy A differs from therapy B, or therapy A does not differ from therapy B. The two rows represent our decision: we conclude either that they differ or that they do not differ. In this figure, the four possibilities that were just listed are represented as four cells in a 2 × 2 table. If there is no difference, and on the basis of the samples included in our study we conclude there is no difference, this is a correct decision *(cell a)*. If there is a difference, and on the basis of our study we conclude that there is a difference *(cell d)*, this too is a correct decision.

In the best of all worlds, all of the possibilities would fall into one of these two cells. Unfortunately, this is rarely, if ever, the case. There are times when there is no difference between the therapies, but on the basis of the samples of subjects included in our study, we erroneously conclude that they differ *(cell c)*. This is called a *type I error*. It is also possible that there really is a difference between the therapies, but on the basis of the samples included in our study we erroneously conclude that there is no difference *(cell b)*; this is called a *type II error*. (In this situation, the therapies differ, but we fail to detect the difference in our study samples.)

The *probability* that we will make a type I error is designated α, and the *probability* that we will make a type II error is designated β (as shown in Fig. 11.5).

α is the so-called *P* value, which is seen in many published papers and has been sanctified by many years of use. When you see "$P < .05$," the reference is to α. What does $P < .05$ mean? It tells us that we have

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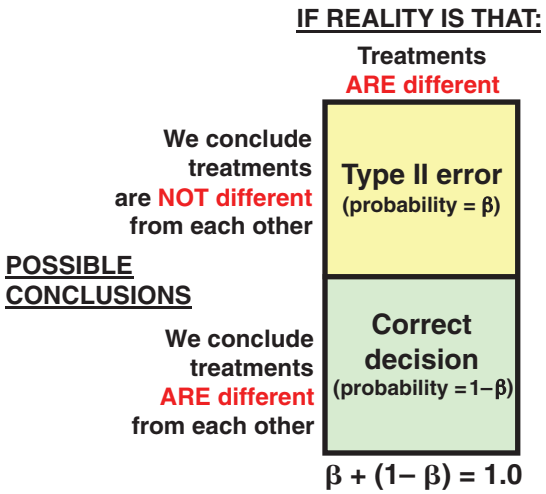

Fig. 11.6 Possible outcomes of a randomized trial when the treatments differ.

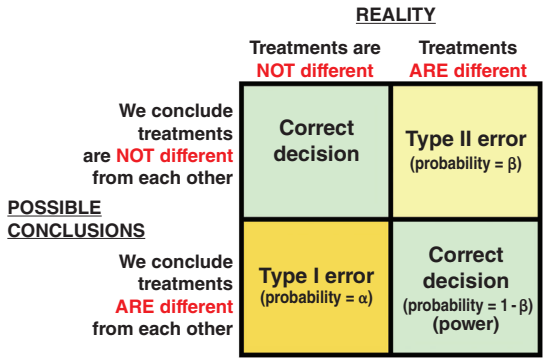

Fig. 11.7 Possible outcomes of a randomized trial: summary.

TABLE 11.1 Summary of Terms

Term	Definitions
α	= Probability of making a type I error = Probability of concluding the treatments differ when in reality they do not differ
β	= Probability of making a type II error = Probability of concluding that the treatments do not differ when in reality they do differ
Power	= 1 − Probability of making a type II error = 1 − β = Probability of correctly concluding that the treatments differ = Probability of detecting a difference between the treatments if the treatments do in fact differ

concluded that therapy A differs from therapy B on the basis of the sample of subjects included in our study, which we found to differ. The probability that such a difference could have arisen by chance alone, and that this difference between our groups does not reflect any true difference between therapies A and B, is only 0.05 (or 1 in 20).

Let's now direct our attention to the right half of this 2 × 2 table, which shows the two possibilities when there is a true difference between therapies A and B, as shown in Fig. 11.6. If, as seen here, the reality is that there is a difference between the therapies, there are only two possibilities: (1) We might conclude, in error, that the therapies do not differ (type II error). The probability of making a type II error is designated β. Or (2) we might conclude, correctly, that the therapies differ. Because the total of all probabilities must equal 1 and the probability of a type II error = β, the probability that we will correctly decide on the basis of our study that the therapies differ if there is a difference will equal 1 − β. This probability, 1 − β, is called the *power* of the study. It tells us how good our study is at correctly identifying a difference between the therapies if in reality they are different. How likely is our study not to miss a difference if one exists?

The full 2 × 2 table in Fig. 11.7 includes all of the terms that have been discussed. Table 11.1 provides multiple definitions of these terms that are commonly used in the epidemiologic literature.

How do these concepts help us to arrive at an estimate of the sample size that we need? If we ask the question, "How many people do we have to study in a clinical trial?," we must be able to specify a number of items as listed in Box 11.2.

First, we must specify the expected difference in response rate. Let's say that the existing therapy cures 40% of patients, and we are going to test a new therapy. We must be able to say whether we expect the new therapy to cure 50%, 60%, or some other proportion of treated patients. That is, will the new therapy be 10% better than the current therapy and cure 50% of people, 20% better than current therapy and cure 60%, or some other difference? What is the size of the difference between current therapy and new therapy that we want to

Box 11.2 What Must Be Specified to Estimate the Sample Size Needed in a Randomized Trial?

1. The difference in response rates to be detected
2. An estimate of the response rate in one of the groups
3. Level of statistical significance (α)
4. The value of the power desired ($1 - \beta$)
5. Whether the test should be one-sided or two-sided

be able to detect with our study? Does the size of the difference make clinical sense?

How do we generally arrive at such an estimate of how much better the new therapy will be? What if we do not have information on which to base an estimate of the improvement in effectiveness that might be anticipated? Perhaps we are studying a new therapy for which we have no prior experience. One approach is to search for data in human populations for similar diseases and therapies. We can also search for relevant data from animal studies. At times, we simply have no way of producing such an estimate. In this situation, we can make a guess (say, 30% improvement) but *bracket* the estimate—that is, calculate the sample size needed based on a 40% improvement in response rate and also calculate the sample size needed based on a 20% improvement in response rate. This is sometimes referred to as a "sensitivity analysis."

Second, we must have an estimate of the clinical outcome (rate of cure, rate of improvement) in one of the groups. In the example just used, we said the current cure rate is 40%. This is the estimate of the response rate for the current treatment group based on current clinical experience.

Third, we must specify the level of α with which we will be satisfied. The choice is up to the investigator; there is nothing sacred about any specific value, but values of 0.05 or 0.01 are commonly used in research.

Fourth, we must specify the power of the study. Again, no specific value is sacred, but powers of 80% or 90% are commonly used. We do not want to miss a difference if one exists!

Finally, we must specify whether the test should be one-sided or two-sided. What does this mean? Our present cure rate is 40%, and we are trying a new therapy that we believe will have a higher cure rate—perhaps 50% or 60%. We want to detect a difference that is in the direction of improvement with the new therapy—an increase in cure rate. So, we might say we will only test for a difference in that direction (improvement) because that is the direction in which we are interested—that is, a one-sided test.

The problem is that in the history of medicine and of public health we have at times been surprised to find that new therapies that we thought would be beneficial have actually been harmful or may lead to significant side effects. If such a possibility exists, we would want to find a difference in cure rate *in either direction* from the current rate in our study—that is, we would use a two-sided test, not only testing for a difference that is better than the current cure rate but also allowing for one that is worse than the current rate. Clinicians and other investigators often prefer to use a one-sided test in their studies because such tests require smaller sample sizes than two-sided tests. Because the number of patients available for study is often limited, a one-sided test is attractive. At times investigators may make a practical decision to use a one-sided test, even if there is no conceptual justification for this decision.

Opinions differ on this subject. Some believe that if the investigator is only interested in one direction—improvement—a one-sided test is justified. Others believe that as long as the difference could go in either direction, a two-sided test is required. In a situation in which a particular disease is currently 100% fatal, any difference with a new therapy could only be in the direction of improvement, then a one-sided test would be appropriate.

Let's now turn to the application of these five factors to estimate the needed sample size from a sample size table. Tables 11.2 and 11.3 are selections from sample size tables published by Gehan in 1979.[1] (Similar tables are available as appendices in standard statistics textbooks.) Both tables give the number of patients needed *in each group* to detect various differences in cure rates with an α of 0.05 and a power ($1 - \beta$) of 0.80. Table 11.2 is intended to be used for a two-sided test and Table 11.3 for a one-sided test.

Let's say that we are conducting a clinical trial of two therapies: one that is currently in use (the "standard of care") and one that is new. The current therapy has a cure rate of 40%, and we believe that the new therapy may have a cure rate of 60%—that is, we wish to detect an improvement in cure rate of 20%. How many subjects do we have to study? Let's say we will use an α of

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TABLE 11.2 Number of Patients Needed in Each Group to Detect Various Differences in Cure Rates; $\alpha = 0.05$; Power $(1 - \beta) = 0.80$ (Two-Sided Test)

Lower of the Two Cure Rates	DIFFERENCES IN CURE RATES BETWEEN THE TWO TREATMENT GROUPS													
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70
0.05	420	130	69	44	36	31	23	20	17	14	13	11	10	8
0.10	680	195	96	59	41	35	29	23	19	17	13	12	11	8
0.15	910	250	120	71	48	39	31	25	20	17	15	12	11	9
0.20	1,090	290	135	80	53	42	33	26	22	18	16	12	11	9
0.25	1,250	330	150	88	57	44	35	28	22	18	16	12	11	—
0.30	1,380	360	160	93	60	44	36	29	22	18	15	12	—	—
0.35	1,470	370	170	96	61	44	36	28	22	17	13	—	—	—
0.40	1,530	390	175	97	61	44	35	26	20	17	—	—	—	—
0.45	1,560	390	175	96	60	42	33	25	19	—	—	—	—	—
0.50	1,560	390	170	93	57	40	31	23	—	—	—	—	—	—

(Modified from Gehan E. Clinical trials in cancer research. *Environ Health Perspect.* 1979;32:31.)

TABLE 11.3 Number of Patients Needed in Each Group to Detect Various Differences in Cure Rates; $\alpha = 0.05$; Power $(1 - \beta) = 0.80$ (One-Sided Test)

Lower of the Two Cure Rates	DIFFERENCES IN CURE RATES BETWEEN THE TWO TREATMENT GROUPS													
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70
0.05	330	105	55	40	33	24	20	17	13	12	10	9	9	8
0.10	540	155	76	47	37	30	23	19	16	13	11	11	9	8
0.15	710	200	94	56	43	32	26	22	17	15	11	10	9	8
0.20	860	230	110	63	42	36	27	23	17	15	12	10	9	8
0.25	980	260	120	69	45	37	31	23	17	15	12	10	9	—
0.30	1,080	280	130	73	47	37	31	23	17	15	11	10	—	—
0.35	1,160	300	135	75	48	37	31	23	17	15	11	—	—	—
0.40	1,210	310	135	76	48	37	30	23	17	13	—	—	—	—
0.45	1,230	310	135	75	47	36	26	22	16	—	—	—	—	—
0.50	1,230	310	135	73	45	36	26	19	—	—	—	—	—	—

(Modified from Gehan E. Clinical trials in cancer research. *Environ Health Perspect.* 1979;32:31.)

0.05, a power of 80%, and a two-sided test. We therefore will use Table 11.2. The first column of this table is designated the lower of the two cure rates. As the current cure rate is 40%, and we expect a cure rate of 60% with our new therapy, the lower of the two cure rates is 40%, and we move to that row of the table. We expect the new therapy to have a cure rate of 60%, so the difference in cure rates will be 20%. We therefore move down the 20% column (the difference in cure rates) to the point at which it intersects the row of 40% (the lower of the cure rates), where we find the value 97. We need 97 subjects *in each of our study groups.*

Another approach is to use the table in a reverse direction. For example, let's consider a clinic for people who have a certain rare disease. Each year the clinic treats 30 patients with the disease and wishes to test a new therapy. Given this maximum number of 30 patients, we could ask, "What size difference in cure rates

could we hope to detect?" We may find a difference of a certain size that may be acceptable, or we may find that the number of subjects available for study is simply too small. If the number of patients is too small, we have several options: We can decide not to do the study, and such a decision should be made early on, before most of the effort has been invested; or we could decide to extend the study in time to accumulate more subjects. Finally, we could decide to collaborate with investigators at other institutions to increase the total number of subjects available for the study. In a study that uses only a single site, any biases in selecting participants may be difficult to identify, but in a multicenter study, the presence of any such bias at one of the centers would be more readily detectable.

This section has demonstrated the use of a sample size table. Formulas and computer programs are also available for calculating sample size. Sample sizes can be calculated not only for randomized trials but also for cohort and case-control studies, as discussed earlier.

RECRUITMENT AND RETENTION OF STUDY PARTICIPANTS

A major challenge in the conduct of randomized trials is to recruit a sufficient number of eligible and willing volunteers. Failure to recruit a sufficient number of volunteers can leave a well-designed trial without enough participants to yield statistically valid results. Potential participants must also be willing to be randomized for the trial. Trials may be significantly delayed by this problem of limited recruitment, and the costs of completing such trials may be increased, since it may take longer to do the overall study. However, given the pressures to recruit a sufficient number of participants, a high level of vigilance is needed to be sure that no coercion, either overt or covert, has been used by study investigators, consciously or subconsciously, to convince possible participants to enroll in a study. Within the limits of a randomized trial, participants must be fully informed of the risks and what arrangements have been made for their compensation if untoward effects should occur. Appropriate arrangements must also be made to cover participants' expenses, such as transportation, accommodations if needed, and the participants' time, particularly if participation is associated with loss of income. However, payment of cash incentives to prospective volunteers will often risk subtle or overt coercion; biases and distortion of the study results may occur, particularly if large incentives are paid.

At times, enrollment as a participant in a study has been marketed to potential volunteers on the basis that only through participation will a participant have a chance of being treated with the newest available treatments. However, the justification for conducting a randomized trial is that we do not know which therapy is better. It is therefore critical that the persons conducting the trial avoid being overly zealous in promising the participants benefits that have not yet been conclusively demonstrated to be associated with the therapy being tested. Institutional Review Boards oversee all of the ethical issues involved in research studies, and no research participants can be recruited until the research protocol is approved.

A related problem is that of retaining volunteers for the full duration of the study. Losses to follow-up and other forms of noncompliance can make this issue a major concern. Participants may lose interest in the study over time, or find participation too inconvenient, particularly over the long term (such as years of follow-up). Investigators must develop an appreciation of why participants often drop out of studies and develop appropriate measures to prevent losses to follow-up.

WAYS OF EXPRESSING THE RESULTS OF RANDOMIZED TRIALS

The results of randomized trials can be expressed in a number of ways. The risks of death or of developing a disease or complication in each group can be calculated, and the *reduction in risk* (efficacy) can then be calculated. *Efficacy* of an agent being tested, such as a vaccine, can be expressed in terms of the rates of developing disease in the vaccine and placebo groups:

$$\text{Efficacy} = \frac{\left(\begin{array}{l}\text{Rate in those who}\\ \text{received the placebo}\end{array}\right) - \left(\begin{array}{l}\text{Rate in those who}\\ \text{received the vaccine}\end{array}\right)}{\text{Rate in those who received the placebo}}$$

This formula tells us the extent of the reduction in disease by use of the vaccine. Risks are often calculated per *person-years* of observation.

Efficacy, or how well a treatment works under "ideal" conditions (such as that in a clinical trial), may

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be differentiated from effectiveness, or how well a treatment works in "real-life" situations. Although randomized trials most often evaluate efficacy of a treatment, the two terms (efficacious and effective) are often (wrongly) used interchangeably. Efficacy and effectiveness will be discussed later.

Another approach to reporting results from randomized trials is to calculate the *ratio of the risks* in the two treatment groups (the relative risk), which will be discussed later. In addition, we often compare the *survival curves* for each of the groups, as we previously illustrated, to determine whether they differ significantly.

A major objective of randomized trials is to have an impact on the way clinical medicine and public health are practiced. But at times practitioners may find it difficult to place the findings of such trials in a perspective that seems relevant to their practices. Another approach, therefore, for expressing the results of randomized trials is to estimate the *number of patients who would need to be treated* (NNT) to prevent one adverse outcome such as one death. This can be calculated by:

$$\text{NNT} = \frac{1}{\left(\begin{array}{l}\text{Rate in}\\ \text{untreated group}\end{array}\right) - \left(\begin{array}{l}\text{Rate in}\\ \text{treated group}\end{array}\right)}$$

Thus if, for example, the mortality rate in the untreated group is 17% and mortality in the treated group is 12%, we would need to treat:

$$\frac{1}{17\% - 12\%} = \frac{1}{0.05} = 20$$

people to prevent one death. Estimates of NNT are usually rounded up to the next highest whole number. This approach can be used in studies of various interventions, including both treatment and prevention.

For example, as mentioned in Chapter 10, in the European Randomized Study of Screening for Prostate Cancer, there was a reduction of about 27% in prostate cancer mortality.[2] Thus if in 100 screened individuals 27 prostate cancer deaths were avoided, screening would have to be conducted in ($100 \div 27 = 1 \div 0.27$) 4 individuals in order to prevent 1 prostate cancer death. The same approach can also be used to look at the risk of side effects by calculating the *number needed to harm* (NNH) to cause one additional person to be harmed. These estimates are subject to considerable error and are generally presented with 95% confidence intervals so that they can be properly interpreted. In addition, they have other limitations: they do not take into account quality of life and are of limited value to patients. These estimates can nevertheless help practitioners to estimate the size of the effect they might expect to observe by using the new treatment or preventive measure in their practices.

INTERPRETING THE RESULTS OF RANDOMIZED TRIALS

Generalizability of Results Beyond the Study Population

Whenever we carry out a trial, the ultimate objective is to generalize the results beyond the study population itself. Let's consider an example. Suppose we want to evaluate a new drug for lupus erythematosus (a connective tissue disease) using a randomized trial. The diagrams in Fig. 11.8 represent a randomized trial in which a defined population is identified from a total population, and a subset of that defined population is the study population. For example, the *total population* might be all patients with lupus erythematosus, the *defined population* might be all patients with lupus erythematosus in our community, and the *study population* could be patients with the disease who receive their medical care from one of several clinics in our community.

If we carry out a study in patients recruited from several clinics in our community and find a new therapy to be better than a therapy that is currently used (the standard of care), we would like to be able to say that the new therapy is better for the disease regardless of where the patients are treated, and not just for patients in those clinics. Our ability to apply the results obtained in our study population to a broader population is called the *generalizability*, or *external validity*, of the study. We want to be able to *generalize* from the study findings to all patients with the disease in our community. To do so, we must know to what extent the patients we have studied are representative of the defined population—that is, of all patients with the disease in question in our community (see Fig. 11.8A). We must characterize those who did not participate in the study and identify characteristics of study patients that might differ from those in patients who did not participate in the study. Such differences may preclude our generalizing the results of

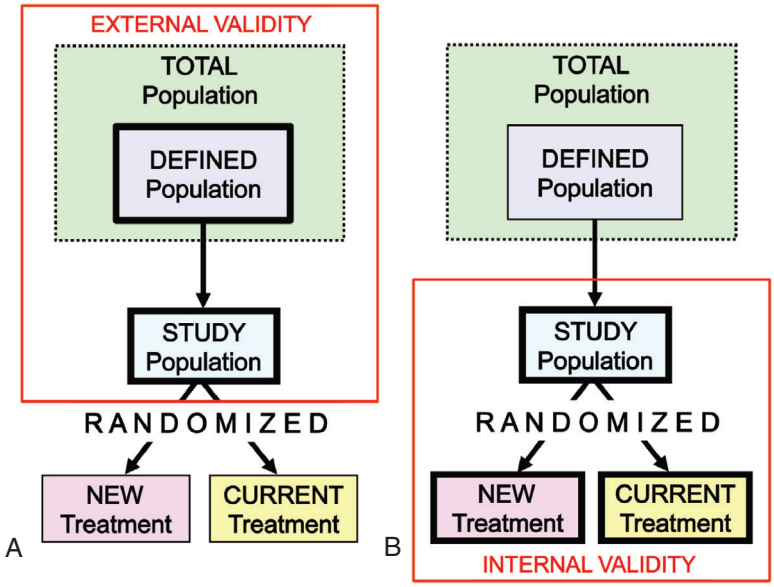

Fig. 11.8 **(A)** External validity (generalizability) in a randomized trial. Findings of the study are generalizable from the study population to the defined population and, presumably, to the total population. **(B)** Internal validity in a randomized trial. The study was done properly, and the findings of the study are therefore valid in the study population.

the study to other patients who were not included in the study. We may also wish to generalize our results, not just to all patients with the disease in our community, but to all patients with the disease, regardless of where they live—that is, to the total population of patients with the disease. Rarely, however, is the total population for a randomized trial known (let alone enumerated). Although it is hoped that the defined population is representative of the total population, this assumption is rarely, if ever, verified.

External validity should be distinguished from *internal validity* (see Fig. 11.8B). A randomized trial is *internally valid* if the randomization has been properly done and the study is free of other biases and is without any of the major methodologic problems that have been discussed. Essentially it should be ideally concluded that the observed differences in the outcomes in the two groups being compared are attributed to the hypothesized exposure under study, aside from sampling errors. Randomized trials are considered the gold standard of study designs because randomization, if correctly conducted, prevents biases on the part of the study investigators from influencing the treatment assignment for each patient. If our study is sufficiently large, randomization will also most likely lead to comparability between treatment groups on factors that may be important for the outcome, such as age, sex, race, and so on, as well as for factors we have not measured or may not even be aware of as important. The issues of internal validity and of external validity (generalizability) are basic concerns in the conduct of any randomized trial and in observational study designs, discussed in prior chapters. Because randomized trials usually study volunteers, their external validity tends to be lower than that of observational studies. The opposite is true for internal validity, given that comparability between groups is much more likely in clinical trials.

What Can the Results of a Randomized Trial Tell a Treating Physician About an Individual Patient?

Let's consider a simple hypothetical scenario. A physician is about to prescribe a treatment for one of her patients. The physician is familiar with a recently published high-quality randomized trial that compared Therapy A to Therapy B for the condition with which her patient presents (Fig. 11.9A). As seen in the diagram, in the trial, a much greater proportion of patients

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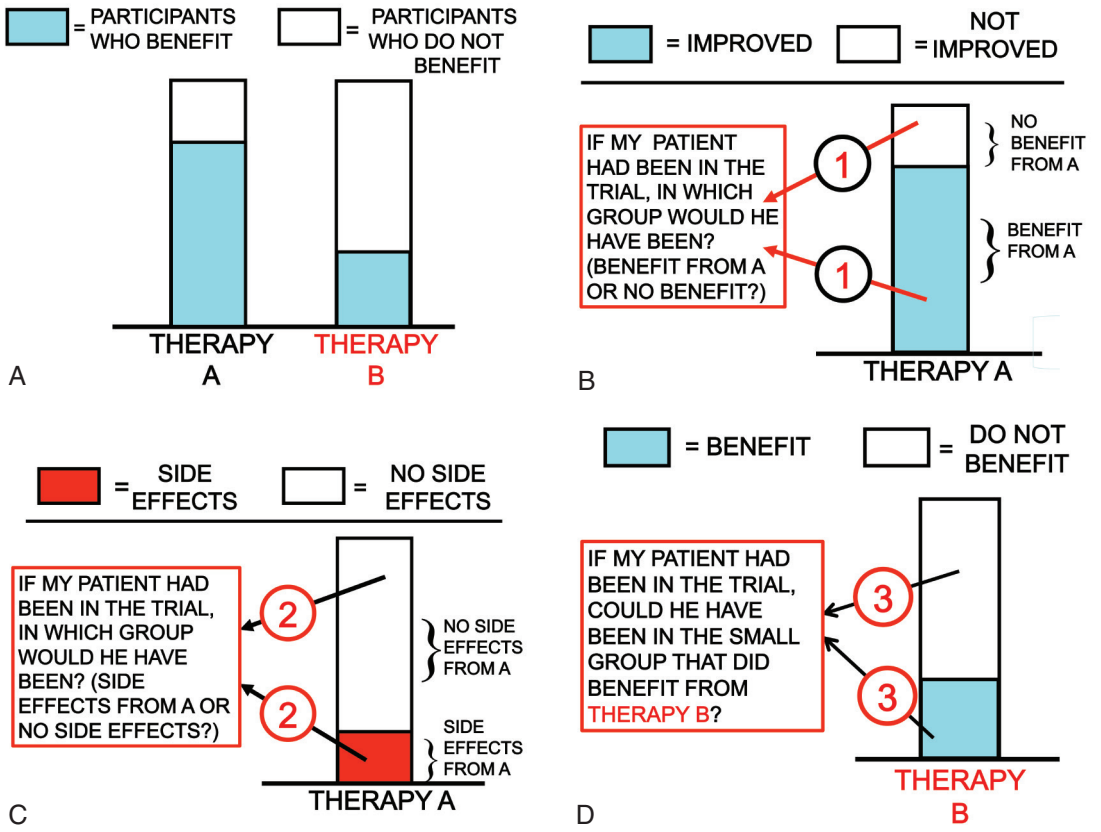

Fig. 11.9 **(A)** Results of a hypothetical randomized trial comparing Therapy A with Therapy B. Blue areas indicate numbers of patients who benefited from each therapy, and white areas indicate those who did not respond to each therapy. **(B)** Physician's first question. **(C)** Physician's second question. **(D)** Physician's third question. (See explanation in text below.)

who received Therapy A had a good result (blue portions of the bars) than the proportion of patients who had a good result who received Therapy B. The trial results were therefore reported as showing that Therapy A is superior to Therapy B for this condition.

The physician is well aware of the results reported for the randomized trial. However, before prescribing therapy for her patient on the basis of reported trial results, the physician has a few questions she would like to have answered, which could provide her with valuable guidance for selecting the better therapy *for this patient*. Only three of her questions will be listed here as examples:

1. "If my patient had participated in the randomized trial and had been in the group that was randomized to receive Therapy A (see Fig. 11.9B), would he have been among those who improved (shown in blue) or would he have been among those who did not respond to Therapy A (the top white part of the bar)?"
2. "If my patient had been a participant in the randomized trial and had been in the group that received Therapy A (see Fig. 11.9C), would he have been among those who developed side effects (shown in red) or would he have been among those who did not show any side effects from Therapy A (the top white part of the bar)?"
3. "If my patient had been a participant in the randomized trial and had been in the group receiving Therapy B (see Fig. 11.9D), would he have been in the group who improved after receiving Therapy B (shown in blue) or would he have been among those

who did not respond to Therapy B (the top white part of the bar)?"

Unfortunately, most randomized trials do not provide the information the physician would need to characterize an individual patient sufficiently to predict what responses her patient might have to the therapies available. She is generally not given enough information to tell her whether it would be reasonable for her to generalize from the randomized trial results to a specific patient before selecting and initiating treatment. If she does generalize to her patient, from which subgroup of participants in the trial should she generalize?

Another limiting factor in many randomized trials is that even if we assume that dropouts from the trial were kept to a minimum and that the participants had all agreed to be randomized, the question remains: Can we assume that in the "real" nonrandomized world, a given patient would respond in the same way that a randomized patient might respond in a trial? What do we know about the personalities and preferences of participants in randomized trials that would indicate to us if a specific patient to be treated has similar characteristics including the same values, personality, and concerns? Is a person who agrees to be randomized similar to a general population from which a specific patient may have come for treatment? As David Mant pointed out, participants in randomized trials are usually not representative of the general population.[3] Participants in trials are generally healthier, younger, and better educated than people coming in for treatment. A final question to address is whether we have lost our concern about individuals when we reduce everyone in a study to being part of a study group, often only examining the results for the group as a whole but losing sight of individual differences and preferences.

Comparative Effectiveness Research

Some randomized trials are designed to compare a new therapy to a placebo. Other randomized trials focus on comparing a new treatment with an older accepted treatment in order to determine whether the new treatment is superior to the established treatment. Two examples of trials used for evaluating widely accepted interventions are discussed later in this chapter. In recent years, interest has also developed in what has been termed comparative effectiveness research (CER), in which two or more existing interventions are compared in order "to determine which intervention would work best in a given population or for a given patient."[4] In this type of approach, results from other types of study designs, which are discussed in prior chapters, may be used together with the findings of randomized trials to try to answer these questions.

Another issue relates to the costs of interventions. For example, many treatments of human immunodeficiency virus (HIV) infections are very expensive, and such treatments may be affordable in high-income countries but may not be affordable in many low- and middle-income countries. As newer and less expensive (generic) medications are developed, studies are often conducted to determine whether the newer, less expensive alternatives are as effective as the more expensive interventions whose effectiveness has already been documented. Such studies are often referred to as *equivalence studies* and are designed to determine whether the less expensive interventions are as effective as the more expensive treatments. The term *noninferiority studies* has also been used for such evaluations. These studies should be distinguished from *superiority studies,* in which newly developed agents are evaluated to determine whether they are more effective (superior) than currently available interventions.

FOUR PHASES IN TESTING NEW DRUGS IN THE UNITED STATES

As new drugs are developed, the US Food and Drug Administration (FDA) follows a standard sequence of four phases for testing and evaluating these new agents:

Phase I trials: These trials are clinical pharmacologic studies—small studies of 20 to 80 patients that look at safety issues with the new drug or other treatment. Toxic and pharmacologic effects are examined, including safety, safe ranges of human dosage, and the side effects observed with the new treatment. If the drug passes these studies, it then undergoes *phase II* studies.

Phase II trials: Phase II studies consist of clinical investigations of 100 to 300 patients in order to evaluate the efficacy of the new drug or treatment and to further assess its relative safety. If the drug passes phase II studies, it is then tested in *phase III* trials.

Phase III trials: These studies are large-scale randomized controlled trials for efficacy and relative safety. These studies often include 1000 to 3000 or more

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participants. Recruiting such large numbers of participants may be very difficult and often necessitates recruiting from more than one study center. When recruitment difficulties are anticipated from the beginning, the study may be designed in its planning stage as a multicenter trial. If the drug passes phase III testing, it can be approved and licensed for marketing.

Phase IV studies: It has been increasingly recognized that certain adverse effects of drugs, such as carcinogenesis (cancer) and teratogenesis (congenital malformations), may not become manifest for many years. It is also possible that such adverse effects of new drugs may be so infrequent that they may not be detectable even in relatively large randomized clinical trials, but may become evident only when the drug is in use by large populations after marketing has begun. For this reason, *phase IV* studies, which are also called *postmarketing surveillance*, are important for monitoring new agents as they come into general use by the public. Phase IV studies are not randomized studies and are not really trials at all, unlike phase I, II, and III trials. Since phase IV studies ascertain side effects of a new treatment after the drug has been marketed, participants are not randomized. For the findings from such postmarketing surveillance to be valid, a very high-quality system for reporting of adverse effects is essential. While the focus of phase IV studies is often on the numbers of side effects reported and the number of people who received the new agent and developed side effects, phase IV studies are often very valuable in providing additional evidence on benefits and to help optimize the use of the new agent.

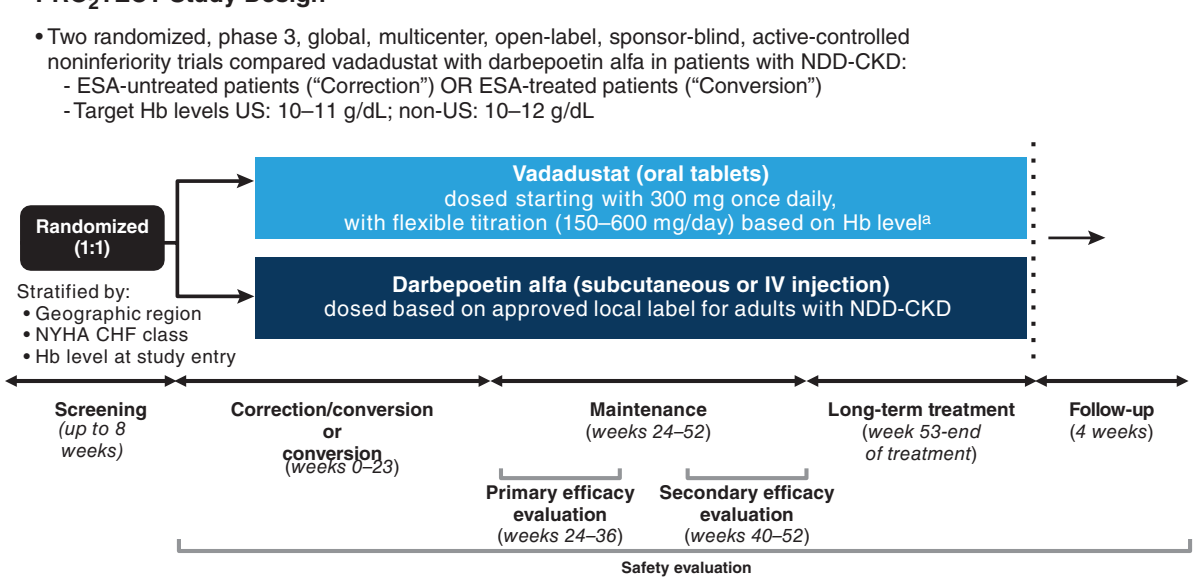
The rigorous sequence described above has protected the American public against many hazardous agents. In recent years, however, pressure to speed up the processing of new agents for treating HIV and acquired immunodeficiency syndrome (AIDS) has led to a reexamination of this approval process. It seems likely that whatever modifications are ultimately made in the approval process will not remain limited to drugs used against AIDS but will in fact have extensive ramifications for the general process of approving new drugs. The changes made in the future will therefore have major implications for the health of the public both in the United States and throughout the world.

THREE MAJOR RANDOMIZED TRIALS AND CLINICAL DEVELOPMENT PROGRAMS IN THE UNITED STATES

Vadadustat for the Treatment of Anemia of Chronic Kidney Disease

In 2019, Gregg L. Semenza (Johns Hopkins), William G. Kaelin Jr. (Harvard), and Sir Peter J. Ratcliffe (Oxford) were jointly awarded the Nobel Prize in Physiology or Medicine "for their discoveries of how cells sense and adapt to oxygen availability."[5] They discovered a transcription factor, Hypoxia Inducible Factor, or HIF, that is responsible for regulating oxygen homeostasis in response to hypoxia.

Vadadustat is a Hypoxia Inducible Factor-prolyl hydroxylase inhibitor (HIF-PHI) that was developed by Akebia Therapeutics, Inc., a US-based biotech company, for the management of anemia in patients with chronic kidney disease (CKD). Several clinical development programs were designed and run globally to seek regulatory authority approvals for vadadustat. In Japan, Akebia partnered with Mitsubishi Tanabe Pharma Corporation (MTPC) to run the studies in Japan given the special regulatory requirements by the Pharmaceuticals and Medical Devices Agency (PMDA). The results of these trials were published[6–10] and presented to the PMDA, which approved and granted the marketing authorization of vadadustat in Japan for the treatment of anemia of chronic kidney disease. Akebia also partnered with Otsuka Pharmaceutical to support the clinical development of vadadustat in the US and the rest of the world, excluding Japan. Akebia designed a global phase III clinical trial program that included four trials of similar design but with different patient populations.[11,12] These trials were designed to test for vadadustat's noninferiority to standard of care in terms of efficacy in terms of raising and maintaining hemoglobin, and cardiovascular safety. The PRO_2TECT program included two trials for patients with non–dialysis-dependent CKD; one trial recruited erythropoietin stimulating agent (ESA)-untreated patients and the other recruited previously ESA-treated patients. The INNOVATE program included two trials for patients with dialysis-dependent CKD; one trial recruited patients new to dialysis (incident trial) and the other recruited patients who have been stable on dialysis (prevalent trial). Each of these trials had similar overarching design (Fig. 11.10). These trials were



[a]Study drug is titrated to achieve target Hb levels (US: 10–11 g/dL; non-US: 10–12 g/dL).
CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agents; Hb, hemoglobin; IV, intravenous; NDD, non–dialysis dependent; NYHA CHF, New York Heart Association Congestive Heart Failure.

Fig 11.10 Schematic design of the PRO_2TECT Clinical Trial Program. It included two randomized, phase 3, global, multicenter, open-label, sponsor-blind, active-controlled noninferiority trials comparing vadadustat with darbepoetin alfa in patients with non–dialysis dependent chronic kidney disease. One trial included erythropoietin stimulating agent (ESA)-untreated patients ("Correction Trial"), the other trial included ESA-treated patients ("Conversion Trial").

conducted in many countries and recruited over 6000 patients overall. The trial results were published in 2021 in the *New England Journal of Medicine*.[13,14] The INNOVATE program met the prespecified noninferiority criteria for both efficacy and cardiovascular safety. The PRO_2TECT program met the prespecified noninferiority criteria for efficacy but failed to meet the prespecified noninferiority criteria for cardiovascular safety. Akebia submitted the new drug application (NDA) to the FDA in 2021, and in 2022 the FDA issued a complete response letter (CRL) to Akebia in which it denied the NDA for vadadustat in the US.[15] Akebia and Otsuka also filed a marketing authorization application (MAA) to the European Medicines Agency (EMA), which approved the use of vadadustat in patients with dialysis-dependent CKD, but not non–dialysis-dependent CKD.[16] Most recently, the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) has granted marketing authorization for vadadustat for the treatment of symptomatic anemia associated with CKD in adults on chronic maintenance dialysis.[17]

Aspirin Dosing for the Prevention of Cardiovascular Events

The use of aspirin has been long recommended for patients with cardiovascular disease to reduce the risk of adverse clinical outcomes by various clinical practice guidelines. However, there has been mixed results from observational studies and randomized trials on the best dose to prevent major adverse cardiovascular events (MACE). The Patient-Centered Outcomes Research Institute (PCORI) funded the ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) trial,[18] published in the New England Journal of Medicine in 2021, which aimed to determine the optimal dosage of aspirin for patients with established atherosclerotic cardiovascular disease.[19] The trial compared the effects of a daily dose of 81 mg

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versus 325 mg of aspirin on outcomes such as death, myocardial infarction, stroke, and major bleeding. Using a pragmatic approach between 2016 and 2019, the study recruited 15,076 patients and used a patient-centric approach, incorporating real-world evidence from electronic health records, and followed them up for 26.2 months. The primary effectiveness outcome (composite of death, hospitalization for myocardial infarction, or hospitalization for stroke) showed no statistically significant difference between the two dosage groups. The primary safety outcome (hospitalization for major bleeding) also showed no statistically significant difference. Adherence to the trial medication was higher in the 81-mg group compared to the 325-mg group. Overall, the study suggests that there is no clear advantage of one dosage over the other in terms of patient outcomes for aspirin use in patients with atherosclerotic cardiovascular disease. The study provides important insights into the optimal dosage of aspirin for this patient population, contributing to the evidence base for clinical decision-making.

Labor Induction Versus Expectant Management in Pregnant Women

The ARRIVE trial (A Randomized Trial of Induction Versus Expectant Management),[20] aimed to investigate whether elective induction of labor at 39 weeks would lead to better outcomes for low-risk nulliparous women compared to expectant management. The trial was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and published in the *New England Journal of Medicine* in 2018.[21] The trial was conducted at 41 hospitals in the United States. The study enrolled 6106 women who were randomly assigned to either the induction group or the expectant-management group. The primary outcome of the trial was a composite variable of perinatal death or severe neonatal complications. The results of this trial demonstrated that women in the induction group had a lower rate of the primary outcome (4.3%) compared to the women in the expectant-management group (5.4%). This difference was statistically significant, indicating that elective induction of labor at 39 weeks reduced the risk of adverse perinatal outcomes. In addition, the trial found that the induction group had a lower rate of cesarean delivery (18.6% vs. 22.2%) and a lower incidence of hypertensive disorders of pregnancy compared to the expectant-management group. Women in the induction group also reported less pain during labor and a higher sense of perceived control during childbirth. Overall, the ARRIVE trial provided evidence supporting the benefit of elective induction of labor at 39 weeks for low-risk nulliparous women. These findings challenged the previous practice of avoiding elective labor induction between 39 weeks and 40 weeks 6 days due to concerns about adverse maternal outcomes and higher rates of cesarean delivery.

REGISTRATION OF CLINICAL TRIALS

It has long been recognized that not all results of clinical trials are published. This can pose a serious problem when the results from all published clinical trials are reviewed. For example, if clinical trials of a new drug are reviewed but only those that show beneficial results have been published and those showing negative results (for some reason) have not been published, an erroneous conclusion that *all* studies of the new drug have shown a clear benefit might be drawn from the published studies. This type of common problem is called *publication bias* or non-publication bias. For example, Liebeskind and colleagues[22] identified 178 controlled clinical trials of acute ischemic stroke reported in English over a 45-year period from 1955 to 1999 through a systematic search of several large databases. These trials enrolled a total of 73,949 subjects and evaluated 75 agents or other types of intervention. They found the issue of publication bias to be an important factor in reviewing the literature on trials of acute ischemic strokes. Trials in which the tested agent was shown to be harmful were substantially more likely *not* to be published than trials in which results indicated the tested agent was neutral or beneficial.

Several factors account for the problem of publication bias. Journals are eager to publish results from studies showing dramatic effects, rather than results from studies showing no benefit from a new drug, device, or other medical intervention. Both researchers and journals appear less interested in studies showing either that a new treatment is inferior to current treatment or that the findings are not clear one way or the other (null findings). An even more important issue is contributing to this problem—companies that develop new drugs and fund studies of these drugs frequently want to keep the results unpublished when they show

no benefits, or show serious side effects, or when the drug studied is shown to be less effective than currently available agents. The companies are clearly concerned that the results of such studies could adversely affect sales of the product and significantly impact the large potential profits they anticipate from the new agent. The net result, however, is concealment of the data, giving a picture of the agent—including its effectiveness and safety—that is not complete, so that regulators, physicians, and the public are prevented from making an evidence-based decision (i.e., a decision based on the total information generated through clinical trials).

The extent of the risk to public health from selective reporting of clinical trials and the frequency with which this selective reporting occurs led the International Committee of Medical Journal Editors to adopt a policy, which became effective in 2005, that *all* clinical trials of medical interventions must be registered in a public trials registry before any participants are enrolled in the study.[23] Medical interventions include drugs, surgical procedures, devices, behavioral treatments, and processes of health care. Registration in a registry accessible to the public at no charge is required before any clinical trial will be considered for publication by the major journals that have agreed to this policy. The federal repository for clinical trials is found at ClinicalTrials.gov on the internet. As of 2017, all NIH-funded clinical trials are expected to register and submit study results to ClinicalTrials.gov, according to the "*NIH Policy on Dissemination of NIH-Funded Clinical Trial Information*" (NOT-OD-16-149).[24]

ETHICAL CONSIDERATIONS

Many ethical issues arise in the context of clinical trials. One frequently raised question is whether randomization itself is ethical. How can we knowingly withhold a drug from patients, particularly those with serious and life-threatening diseases? Randomization is ethical only when we do not know whether drug A is better than drug B. We may have some indication that one treatment is better than the other (and often this is the rationale for conducting a trial in the first place), but we are not certain. Often, however, it is not clear at what point we "know" that drug A is better than drug B. The question may be better stated as, "When do we have adequate evidence to support the conclusion that drug A is better than drug B?" One question that has received considerable attention in recent years is whether it is ethical to use a placebo.[25] Implicit in this question is the issue of whether it is ethical to withhold a treatment that has been shown to be effective.[26]

The question can also be posed in the reverse: "Is it ethical not to randomize?" When we are considering drugs, preventive measures, or systems of health care delivery that apply to large numbers of people, both in the United States and in other countries, the mandate may be to carry out a randomized trial to resolve questions of benefit and harm, and not to continue to subject people to unnecessary toxic effects and raise false hopes, often at tremendous expense. Hence the question about the ethics of randomization should be asked in both directions: randomizing and not randomizing.

Another important question is whether truly informed consent can be obtained in studies. Many protocols for multicentered clinical trials require that patients be entered into the study immediately after diagnosis. The patient may be incapable of giving consent at that time, and the family may be so shocked by the diagnosis that has just been received and by its implications that they have great difficulty in dealing with the notion of randomization and agreement to be randomized. For example, much of the progress of recent decades in the treatment of childhood leukemia has been a result of the rigorous multicentered protocols that have required enrollment of the child immediately after the diagnosis of leukemia has been made. Clearly, at such a time the parents are so distressed that one may question whether they are capable of giving truly informed consent. Nevertheless, only through such rigorous trials has the progress been made that has saved the lives of so many children with acute leukemia.

Finally, under what circumstances should a trial be stopped earlier than originally planned? This is also a difficult issue and may arise because either harmful effects or beneficial effects of the agent become apparent early, before the full sample has been enrolled, or before subjects have been studied for the full follow-up period. In many studies, an outside data and safety monitoring board reviews the data as they are received, and the board makes that decision, as seen, for example, in the Physicians' Health Study discussed in Chapter 10, in which two medications were simultaneously tested in a factorial design: aspirin was tested for primary prevention of cardiovascular disease and beta carotene for primary prevention of cancer. The external data

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monitoring board decided that the findings for aspirin were sufficiently clear that the aspirin part of the study should be terminated but that the beta carotene portion of the study should be continued.

SYSTEMATIC REVIEWS AND META-ANALYSIS

Each clinical or public health research question is usually being addressed by several investigators who conduct multiple research studies. The evidence generated from these studies does not always have the same methods, rigor, and even results. The systematic review is a valuable methodology to identify all the published research studies on a particular research question, asses the rigor of the methods, known as risk of bias assessment, and then qualitatively summarize the evidence. Systematic reviews follow an explicit and detailed protocol of prespecified research question, search criteria, sources of articles from bibliographic databases, and analysis methods. Such protocols are commonly registered in an international registry like the International Prospective Register of Systematic Reviews (PROSPERO). Such registration allows the scientific community to anticipate the upcoming results of a systematic review, and avoid duplicating the work by other research groups, and provides the platform for transparency of the methods which facilitates reproducibility and future update of the systematic review.

An optional follow-up component could be the meta-analysis, which is the quantitative summary of the effect estimate in each of the individual studies. Systematic reviews and meta-analyses were traditionally developed and used for summarizing the evidence from clinical trials to answer questions related to the efficacy, effectiveness or safety of an intervention compared with another intervention or standard of care. However, there has been an increasing use of systematic reviews and meta-analyses for other study designs as well. One example to discuss here is a recently published systematic review and meta-analysis by Zou et al. in the *Annals of Internal* Medicine.[27] Sodium–glucose cotransporter-2 inhibitors (SGLT2i) is a new class of medications (the first was approved in 2012) to provide glycemic control in patients with type 2 diabetes mellitus. Several other agents were later approved by the FDA and other regulatory authorities. The sponsoring pharmaceutical companies of these drugs tested the efficacy of these drugs for other indications like reducing the risk of heart failure in patients with type 2 diabetes. After the publication of the primary results of these trials, the need arose to summarize the evidence from all these trials in one study. Zou et al. systematically identified six clinical trials that met the inclusion criteria and quantitatively summarized the evidence. They found that SGLT2i reduced the risk of hospitalization for heart failure by 37% (95% confidence interval (CI), 25% to 47%) at 6 months, 32% (95% CI, 20% to 42%) at 1 year, and 26% (95% CI, 10% to 40%) at 2 years (Fig. 11.11). They concluded that the absolute benefit of the use of SGLT2i is more pronounced in the first year, but also highlighted the increased risk for genital infections of those receiving SGLT2i.

CONCLUSION

The randomized trial is the gold standard for evaluating the efficacy of therapeutic, preventive, and other measures in both clinical medicine and public health. This chapter and Chapter 10 have provided an overview of approaches to study design in randomized trials and the measures used to minimize or avoid selection and other types of bias. From a societal viewpoint, generalizability and ethical concerns are major considerations, and these issues have been discussed.

EPILOGUE

We conclude this discussion of randomized trials by citing an article by Caroline and Schwartz, which was published in the journal *Chest* in 1975. The article was titled "Chicken Soup Rebound and Relapse of Pneumonia: Report of a Case."[28]

The authors introduced their topic by saying:

> *Chicken soup has long been recognized to possess unusual therapeutic potency against a wide variety of viral and bacterial agents. Indeed, as early as the 12th century, the theologian, philosopher and physician, Moses Maimonides wrote, "Chicken soup ... is recommended as an excellent food as well as medication." Previous anecdotal reports regarding the therapeutic efficacy of this agent, however, have*

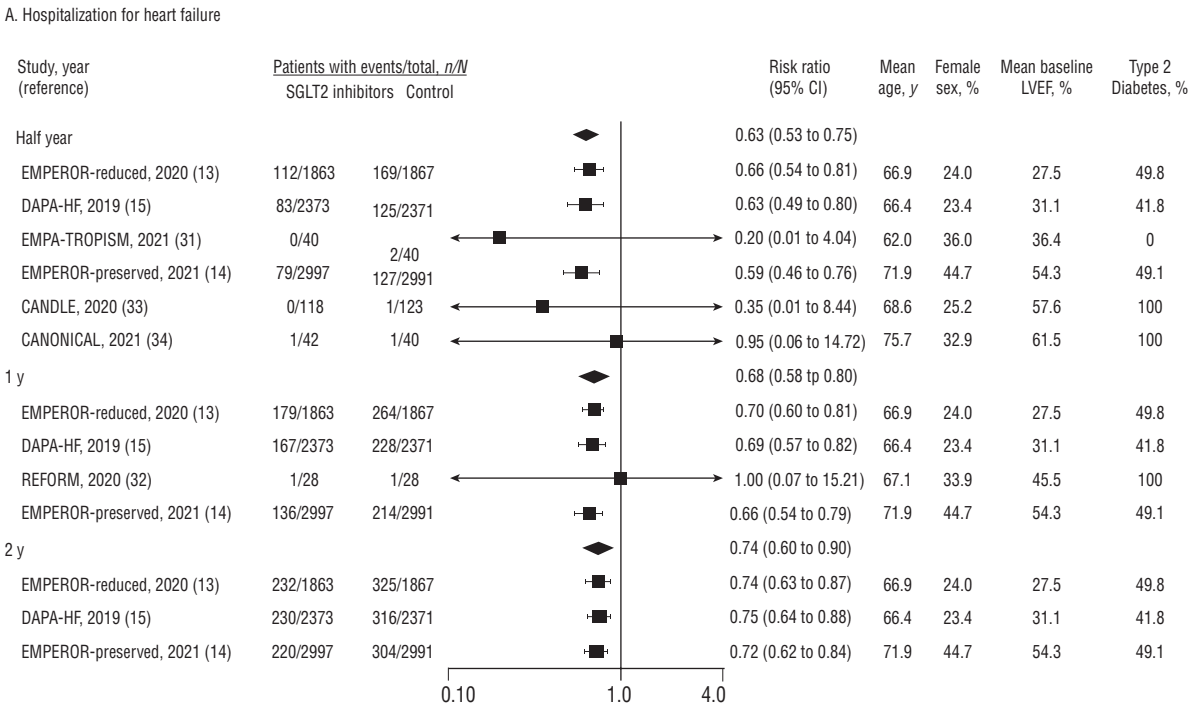

Fig 11.11 Forest plots of time-specific relative risks in 2-stage meta-analyses. *LVEF,* Left ventricular ejection fraction. (From Zou X, Shi Q, Vandvik PO, et al. Sodium-glucose contransporter-2 inhibitors in patients with heart failure: a systematic review and meta-analysis. *Ann Intern Med.* 175(6); 2022: 851-861.)

failed to provide details regarding the appropriate length of therapy. What follows is a case report in which abrupt withdrawal of chicken soup led to a severe relapse of pneumonia.[28]

The authors then present a case report of a 47-year-old physician who was treated with chicken soup for pneumonia. Chicken soup administration was terminated prematurely, and the patient suffered a relapse. Chicken soup being unavailable, the relapse was treated with intravenous penicillin.

The authors' discussion is of particular interest. It reads in part:

The therapeutic efficacy of chicken soup was first discovered several thousand years ago when an epidemic highly fatal to young Egyptian males seemed not to affect an ethnic minority residing in the same area. Contemporary epidemiologic inquiry revealed that the diet of the group not afflicted by the epidemic contained large amounts of a preparation made by boiling chicken with various vegetables and herbs. It is notable in this regard that the dietary injunctions given to Moses on Mount Sinai, while restricting consumption of no less than 19 types of fowl, exempted chicken from the prohibition. Some scholars believe that the recipe for chicken soup was transmitted to Moses on the same occasion, but was relegated to the oral tradition when the scriptures were canonized. ... While chicken soup is now widely employed against a variety of organic and functional disorders, its manufacture remains largely in the hands of private individuals and standardization has proved nearly impossible. Preliminary investigation into the pharmacology of chicken soup (Bohbymycetin) has shown that it is readily absorbed after oral administration. ... Parenteral administration is not recommended.[28]

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This report stimulated several letters to the editor. In one, Dr. Laurence F. Greene, Professor of Urology at the Mayo Clinic, wrote:

> *You may be interested to know that we have successfully treated male impotence with another chicken-derived compound, sodium cytarabine hexamethylacetyl lututria tetrazolamine (Schmaltz [Upjohn]). This compound, when applied in ointment form to the penis, not only cures impotence, but also increases libido and prevents premature ejaculation. ... Preliminary studies indicate that its effects are dose related inasmuch as intercourse continues for 5 minutes when 5% ointment is applied, 15 minutes when 15% ointment is applied, and so forth.*
>
> *We have received a grant in the sum of $650,000 from the National Scientific Foundation to carry out a prospective randomized, controlled double-blind study. Unfortunately, we are unable to obtain a suitable number of subjects inasmuch as each volunteer refuses to participate unless we assure him that he will be a subject rather than a control.*[29]

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REVIEW QUESTIONS FOR CHAPTERS 10 AND 11

1. *The major purpose of random assignment in a clinical trial is to:*
- **a.** Help ensure that study subjects are representative of the general population
- **b.** Facilitate double blinding (masking)
- **c.** Facilitate the measurement of outcome variables
- **d.** Ensure that the study groups have comparable baseline characteristics
- **e.** Reduce selection bias in the allocation of treatment

2. *An advertisement in a medical journal stated that "2000 subjects with sore throats were treated with our new medicine. Within 4 days, 94% were asymptomatic." The advertisement claims that the medicine was effective. Based on the evidence given above, the claim:*
- **a.** Is correct
- **b.** May be incorrect because the conclusion is not based on a rate
- **c.** May be incorrect because of failure to recognize a long-term cohort phenomenon
- **d.** May be incorrect because no test of statistical significance was used
- **e.** May be incorrect because no control or comparison group was involved

3. *The purpose of a* double blind *or* double masked *study is to:*
- **a.** Achieve comparability of treated and untreated subjects
- **b.** Reduce the effects of sampling variation
- **c.** Avoid observer and subject bias
- **d.** Avoid observer bias and sampling variation
- **e.** Avoid subject bias and sampling variation

4. *In many studies examining the association between estrogens and endometrial cancer of the uterus, a one-sided significance test was used. The underlying assumption justifying a one-sided rather than a two-sided test is:*
- **a.** The distribution of the proportion exposed followed a "normal" pattern
- **b.** The expectation before doing the study was that estrogens cause endometrial cancer of the uterus
- **c.** The pattern of association could be expressed by a straight-line function
- **d.** Type II error was the most important potential error to avoid
- **e.** Only one control group was being used

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5. *In a randomized trial, a planned crossover design:*
   - **a.** Eliminates the problem of a possible order effect
   - **b.** Must take into account the problem of possible residual effects of the first therapy
   - **c.** Requires stratified randomization
   - **d.** Eliminates the need for monitoring compliance and noncompliance
   - **e.** Enhances the generalizability of the results of the study
6. *A randomized trial comparing the efficacy of two drugs showed a difference between the two (with a P value* $< .05$*). Assume that in reality, however, the two drugs do not differ. This is therefore an example of the following:*
   - **a.** Type I error (α error)
   - **b.** Type II error (β error)
   - **c.** $1 - \alpha$
   - **d.** $1 - \beta$
   - **e.** None of the above
7. *All of the following are potential benefits of a randomized clinical trial, except:*
   - **a.** The likelihood that the study groups will be comparable is increased
   - **b.** Self-selection for a particular treatment is eliminated
   - **c.** The external validity of the study is increased
   - **d.** Assignment of the next subject cannot be predicted
   - **e.** The therapy that a subject receives is not influenced by either conscious or subconscious bias of the investigator

Number of Patients Needed in an Experimental and a Control Group for a Given Probability of Obtaining a Significant Result (Two-Sided Test)

Lower of the Two Cure Rates	DIFFERENCES IN THE CURE RATES BETWEEN THE TWO TREATMENT GROUPS					
	0.05	0.10	0.15	0.20	0.25	0.30
0.05	420	130	69	44	36	31
0.10	680	195	96	59	41	35
0.15	910	250	120	71	48	39
0.20	1,090	290	135	80	53	42
0.25	1,250	330	150	88	57	44
0.30	1,380	360	160	93	60	44
0.35	1,470	370	170	96	61	44
0.40	1,530	390	175	97	61	44

$\alpha = 0.05$; power $(1 - \beta) = 0.80$.
(Data from Gehan E. Clinical trials in cancer research. *Environ Health Perspect.* 1979;32:31.)

Question 8 is based on the above table.

8. *A drug company maintains that a new drug G for a certain disease has a 50% cure rate as compared with drug H, which has only a 25% cure rate. You are asked to design a clinical trial comparing drugs G and H. Using the preceding table, estimate the number of patients needed in each therapy group to detect such a difference with* $\alpha = 0.05$, two-sided, and $\beta = 0.20$.
   The number of patients needed in each therapy group is _____.

Use your knowledge of study design to answer question 9.

9. *Choose the best study design from the list below for each of the following research questions. Each study design can only be used once.*
   a. Ecologic study
   b. Cross-sectional study
   c. Case-control study
   d. Prospective cohort
   e. Randomized trial

9a. _____ An investigator wishes to determine if the prevalence of syphilis is higher among men than women.

9b. _____ A researcher believes that a rare disease may be associated with use of a common lawn fertilizer.

9c. _____ Health officials in Baltimore City believe that a smoking cessation program in combination with nicotine patches will be more effective than a cessation program alone.

9d. _____ Investigators want to determine the risk of potential health outcomes from heavy drinking among young adults.

9e. _____ A researcher believes that the county-level rate of hospitalization for cardiovascular disease will increase with increasing levels of outdoor air pollution.

Questions 10 and 11 involve the following randomized controlled trial, which explores the effects of a drug in reducing recurrent strokes:

Given the increasing burden of cardiovascular disease, a researcher designs a randomized controlled trial targeting patients who have experienced a stroke within the past 30 days. The trial is testing whether Drug A reduces the likelihood of stroke recurrence compared with the current standard of care (superiority trial). In the trial, 300 stroke patients are randomized into two groups where Group 1 receives Drug A and Group 2 receives standard of care. The investigator compared the cumulative incidence of a recurrent stroke between both groups. Some patients randomized to standard of care obtain Drug A through other means. Meanwhile, some participants randomized to Drug A ended up not taking it. The results from the randomized controlled trial are below:

	GROUP 1 RANDOMIZED TO DRUG A		GROUP 2 RANDOMIZED TO STANDARD OF CARE	
	Took Drug A	Standard of Care	Took Drug A	Standard of Care
Had a recurrent stroke	10	20	5	40
Did not have a recurrent stroke	80	40	15	90

10. *With an intention-to-treat analysis, calculate the cumulative incidence ratio for recurrent stroke using standard of care as the reference. Answers should be rounded to two decimal places.*
Cumulative Incidence Ratio = _____

11. *With a per-protocol analysis, calculate the cumulative incidence ratio for recurrent stroke using standard of care as the reference. Answers should be rounded to two decimal places.*
Cumulative Incidence Ratio = _____

A per-protocol analysis is an interpretation of randomized clinical trial results that removes data from patients who did not comply with the protocol. Compare group 1: 10/90 (those who took drug A as assigned) to group 2: 40/130 (those who received standard of care as assigned). These are the persons who took the drug per protocol (10/90)/(40/130) = 0.36

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12

Estimating Risk: Is There an Association?

LEARNING OBJECTIVES

- To explore the concept of absolute risk.
- To introduce and compare relative risk and odds ratio as measures of association between an exposure and a disease.
- To calculate and interpret a relative risk in a cohort study.
- To calculate and interpret an odds ratio in a cohort study and in a case-control study and to describe when the odds ratio is a good estimate of the relative risk.
- To calculate and interpret an odds ratio in a matched-pairs case-control study.

In the previous chapters, we discussed the basic study designs that are commonly used in epidemiologic investigations. These are shown diagrammatically in Figs. 12.1 through 12.3.

Recall that the fundamental difference between a randomized trial and a cohort study is that, in a cohort study, subjects are not randomly assigned to be exposed or to remain unexposed, because randomization to exposure to possibly toxic or carcinogenic agents clearly would not be acceptable. Otherwise, cohort studies and randomized trials are essentially equivalent. Consequently, cohort studies are used in many studies of etiology because this study design enables us to capitalize on populations that have had a documented specified exposure and to compare them with populations that have not had that exposure. Case-control studies are also used to address questions of etiology, although often at a more exploratory phase. Regardless of which design is used, the objective is to determine whether there is an excess risk (incidence) or perhaps a reduced risk of (or protected from) a certain disease in association with a specified exposure or characteristic. As stated earlier, incidence is a measure of risk of disease. Risk can be defined as the probability of an event (such as developing a disease) occurring.

Before describing these comparative approaches, we will discuss the concept of absolute risk.

ABSOLUTE RISK

The incidence of a disease in a population is termed the *absolute risk*. Absolute risk can indicate the magnitude of the risk in a group of people with a certain exposure, but because it does not take into consideration the risk of disease in unexposed individuals, it does not indicate whether the exposure is associated with an increased risk of the disease. In other words, it is not being compared to another absolute risk. *Comparison is fundamental to epidemiology*. Nevertheless, absolute risk may have important implications in both clinical medicine and public health policy. For example, a woman who contracts rubella in the first trimester of pregnancy and asks her physician, "What is the risk that my child will be malformed?" is given a certain number or percentage as an answer. On the basis of this information, she may decide to abort her pregnancy or to continue her pregnancy. She is not explicitly given comparative data, but an implicit comparison is generally being made: The woman is wondering not only what her risk is, but she also is wondering how that risk compares with what it would have been had she not contracted rubella (this is called the *counterfactual* in causal inference terms, to be discussed later in this book). So, although absolute risk does not stipulate any explicit comparison, an implicit comparison is often made whenever we

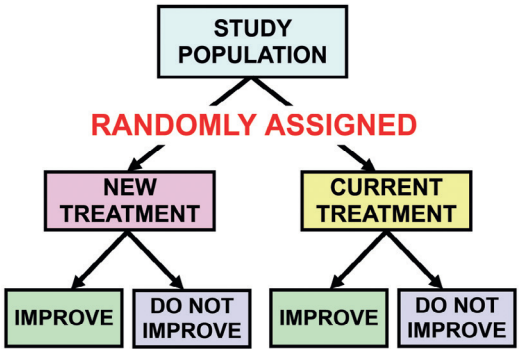

Fig. 12.1 Design of a randomized clinical trial.

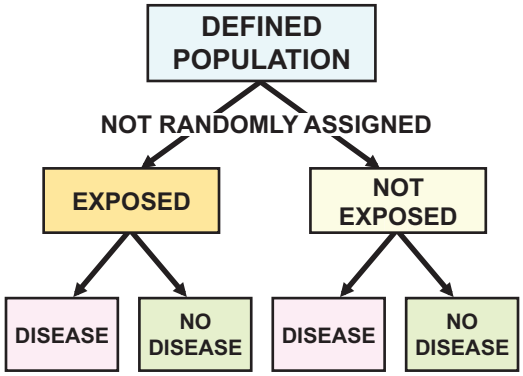

Fig. 12.2 Design of a cohort study.

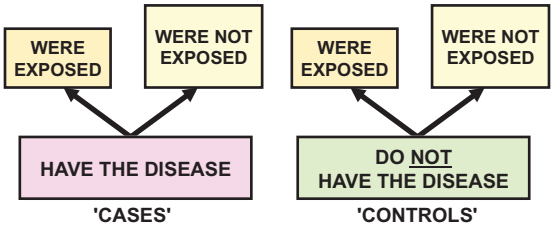

Fig. 12.3 Design of a case-control study.

look at the incidence of a disease. However, to address the question of association, we must use approaches that involve explicit comparisons.

HOW DO WE DETERMINE WHETHER A CERTAIN DISEASE IS ASSOCIATED WITH A CERTAIN EXPOSURE?

To determine whether an association exists between a specified exposure and a particular disease, we must determine, often using data obtained in case-control or cohort studies, whether there is an excess risk of the disease in persons who have been exposed to a certain agent. Let us consider the results of an investigation of a foodborne disease outbreak. The suspect foods were identified, and for each food, the attack rate (or incidence rate) of the disease was calculated for those who ate the food (exposed) and for those who did not eat the food (unexposed), as shown in Table 12.1.

How can we determine whether an excess risk is associated with each of the food items? One approach, shown in column C of Table 12.2, is to calculate the *ratio*

TABLE 12.1 Foodborne Disease Outbreak: I. Percent of People Sick Among Those Who Ate and Those Who Did Not Eat Specific Foods

Food	Ate (% Sick)	Did Not Eat (% Sick)
Egg salad	83	30
Macaroni	76	67
Cottage cheese	71	69
Tuna salad	78	50
Ice cream	78	64
Other	72	50

TABLE 12.2 Foodborne Disease Outbreak: II. Ways of Calculating Excess Risk

Food	(A) Ate (% Sick)	(B) Did not eat (% Sick)	(C) (A)/(B)	(D) (A) − (B) (%)
Egg salad	83	30	2.77	53
Macaroni	76	67	1.13	9
Cottage cheese	71	69	1.03	2
Tuna salad	78	50	1.56	28
Ice cream	78	64	1.21	14
Other	72	50	1.44	22

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of the attack rate of the illness in those who ate each food to the attack rate in those who did not eat the food. (Note that the attack rate is how we call the incidence rate in epidemic situations.) An alternate approach for identifying any excess risk in exposed individuals is shown in column D. We can subtract the risk in those who did not eat the food from the risk in those who did eat the food. The *difference* represents the excess absolute risk in those who were exposed.

Thus, as seen in this foodborne outbreak, to determine whether a certain exposure is associated with a certain disease, we must determine whether there is an excess risk of disease in exposed populations by comparing the risk of disease (in this case food poisoning) in exposed populations to the risk of disease in unexposed populations. We have just seen that such an excess risk can be calculated in the two following ways:

1. The *ratio* of the risks (or of the incidence rates):

$$\frac{\text{Disease risk in exposed}}{\text{Disease risk in unexposed}}$$

2. The *difference* in the risks (or in the incidence rates):

$$\begin{pmatrix}\text{Disease risk}\\ \text{in exposed}\end{pmatrix} - \begin{pmatrix}\text{Disease risk}\\ \text{in unexposed}\end{pmatrix}$$

Does the method that we choose to calculate excess risk make any difference? Let us consider a hypothetical example of two communities, A and B, seen in Table 12.3.

In community A, the incidence of a disease in exposed persons is 40% and the incidence in unexposed persons is 10%. Is there an excess risk associated with exposure? As in the food poisoning example, we can calculate the ratio of the rates or the difference between the rates. The *ratio* of the incidence rates is 4.0. If we calculate the *difference* in incidence rates, it is 30%. In community B, the incidence in exposed persons is 90% and the incidence in unexposed persons is 60%. If we calculate the *ratio* of the incidence of exposed to unexposed persons in population B, it is 90/60, or 1.5. If we calculate the *difference* in the incidence in exposed and unexposed persons in community B it is, again, 30%.

What do these two measures tell us? Is there a difference in what we learn from the ratio of the incidence rates compared with the difference in the incidence rates? This question is the theme of this chapter and Chapter 13.

TABLE 12.3 Example Comparing Two Ways of Calculating Excess Risk

	POPULATION	
	A	B
Incidence (%)		
In exposed	40	90
In unexposed	10	60
Difference in incidence rates (%)	30	30
Ratio of incidence rates	4.0	1.5

RELATIVE RISK

Concept of Relative Risk

Both case-control and cohort studies are designed to determine whether there is an association between exposure to a factor and development of a disease. If an association exists, how strong is it? If we carry out a cohort study, we can put the question another way: "What is the ratio of the risk of disease in exposed individuals to the risk of disease in unexposed individuals?" This ratio is called the *relative risk* (RR):

$$\text{Relative risk} = \frac{\text{Risk in exposed}}{\text{Risk in unexposed}}$$

The relative risk can also be defined as the probability of an event (developing a disease) occurring in exposed people compared with the probability of the event in unexposed people, or as the ratio of these two probabilities.

Interpreting the Relative Risk

How do we interpret the value of a relative risk?

1. If the relative risk is equal to 1, the numerator equals the denominator, and the risk in exposed persons equals the risk in unexposed persons. Therefore, no evidence exists for any increased risk in exposed individuals or for any association of the disease with the exposure in question.
2. If the relative risk is greater than 1, the numerator is greater than the denominator, and the risk in exposed persons is greater than the risk in unexposed persons. This is evidence of a positive association, which may be causal (as discussed in a later chapter).
3. If the relative risk is less than 1, the numerator is less than the denominator, and the risk in exposed

persons is less than the risk in unexposed persons. This is evidence of a negative association, which may be indicative of a protective effect. Such a finding can be observed in people who are given an effective vaccine ("exposed" to the vaccine).

These three possibilities are summarized in Table 12.4.

Calculating the Relative Risk in Cohort Studies

In a *cohort* study the relative risk can be calculated *directly*. Recall the design of a cohort study, seen here in Table 12.5.

TABLE 12.4 Interpreting Relative Risk (RR) of a Disease

If RR = 1	Risk in exposed equal to risk in unexposed (no association)
If RR > 1	Risk in exposed greater than risk in unexposed (positive association; possibly causal)
If RR < 1	Risk in exposed less than risk in unexposed (negative association; possibly protective)

In this table, we see that the incidence in exposed individuals is

$$\frac{a}{a+b}$$

and the incidence in unexposed individuals is

$$\frac{c}{c+d}$$

We calculate the relative risk as follows:

$$\text{Relative risk} = \frac{\text{Incidence in exposed}}{\text{Incidence in unexposed}} = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}$$

Table 12.6 shows a hypothetical cohort study of 3,000 smokers and 5,000 nonsmokers to investigate the relation of smoking to the development of coronary heart disease (CHD) over a 1-year period.

In this example:

$$\text{Incidence among the exposed} = \frac{84}{3{,}000} = 28.0 \text{ per } 1{,}000$$

TABLE 12.5 Risk Calculations in a Cohort Study

		THEN FOLLOW TO SEE WHETHER			
		Disease Develops	Disease Does Not Develop	Totals	Incidence Rates of Disease
First, Select	Exposed	a	b	$a + b$	$\frac{a}{a+b}$
	Not exposed	c	d	$c + d$	$\frac{c}{c+d}$
	$\frac{a}{a+b}$ = Incidence in exposed		$\frac{c}{c+d}$ = Incidence in nonexposed		

TABLE 12.6 Smoking and Coronary Heart Disease (CHD): A Hypothetical Cohort Study of 3,000 Cigarette Smokers and 5,000 Nonsmokers

	CHD Develops	CHD Does Not Develop	Totals	Incidence per 1,000 per Year
Smoke cigarettes	84	2,916	3,000	28.0
Do not smoke cigarettes	87	4,913	5,000	17.4

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and

$$\text{Incidence among the exposed} = \frac{87}{5{,}000} = 17.4 \text{ per } 1{,}000$$

Consequently,

$$\text{Relative risk} = \frac{\text{Incidence in exposed}}{\text{Incidence in unexposed}} = \frac{28.0}{17.4} = 1.61$$

A similar expression of risks is seen in an historical example in Table 12.7, which shows data from the first 12 years of the Framingham Study relating risk of coronary disease to age, sex, and cholesterol level.

First, direct your attention to the upper part of the table, which shows incidence rates per 1,000 population in Framingham by age, sex, and serum cholesterol level. In men the association of risk to cholesterol level seems dose related; risk increases for both age groups with increases in cholesterol level. The relationship is not as consistent in women.

In the lower half of the table, the values have been converted to relative risks. The authors have taken the incidence rate of 38.2 in younger men with low cholesterol levels and assigned it a risk of 1.0; these subjects are considered "unexposed." All other risks in the table are expressed in relation to this risk of 1.0. For example, the incidence of 157.5 in younger men with a cholesterol level greater than 250 mg/dL is compared with the 38.2 incidence rate; by dividing 157.5 by 38.2 we obtain a relative risk of 4.1. Using these relative risks, it is easier to compare the risks and to identify any trends. Although the lowest risk in men has been chosen as the standard and set at 1.0, the authors could have chosen to set any of the values in the table at 1.0 and to make all others relative to it. Thus, when describing the relative risk, the numerator and denominator categories should be specified (e.g., in Table 12.7 the risk of younger men with cholesterol levels ≥250 mg/dL is approximately four times higher than that of younger men whose cholesterol levels are <190 mg/dL). One reason for choosing a low value as the standard is that most of the other values will be greater than 1.0; for most people, the table is easier to read when fewer values are completely to the right of the decimal.

Fig. 12.4 shows data based on merging 2,282 middle-aged men followed for 10 years in the Framingham Study and 1,838 middle-aged men followed for 8 years in Albany, New York. The data relate smoking,

TABLE 12.7 Relationship Between Serum Cholesterol Levels and Risk of Coronary Heart Disease by Age and Sex: Framingham Study During First 12 Years

	MEN		WOMEN	
Serum Cholesterol (mg/dL)	**30–49 Years**	**50–62 Years**	**30–49 Years**	**50–62 Years**
	Incidence Rates (per 1,000)			
<190	38.2	105.7	11.1	155.2
190–219	44.1	187.5	9.1	88.9
220–249	95.0	201.1	24.3	96.3
250+	157.5	267.8	50.4	121.5
	Relative Risks[a]			
<190	1.0	2.8	0.3	4.1
190–219	1.2	4.9	0.2	2.3
220–249	2.5	5.3	0.6	2.5
250+	4.1	7.0	1.3	3.2

[a]Incidence for each subgroup is compared with that of males 30 to 49 years of age, with serum cholesterol levels less than 190 mg/dL (risk = 1.0).

From Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. *J Chronic Dis.* 1967;20:511–524.

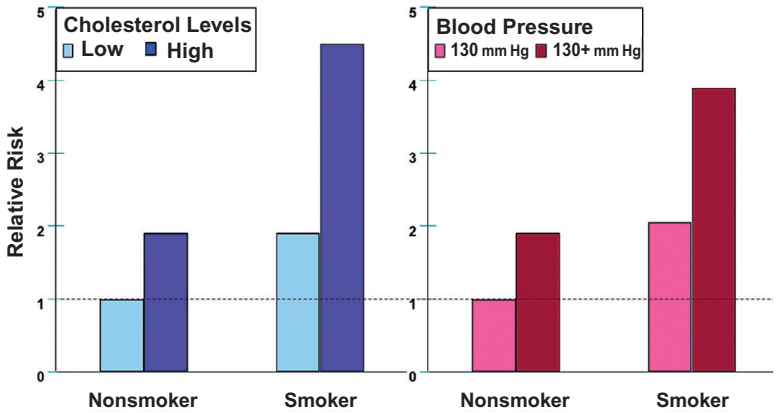

Fig. 12.4 Relative risk for myocardial infarction and death from coronary heart disease in men aged 30 to 62 years by serum cholesterol (left) and blood pressure levels (right) in relation to cigarette smoking. High cholesterol levels are defined as 220 mg/dL or greater. (Data from Doyle JT, Dawber TR, Kannel WB, et al. The relationship of cigarette smoking to coronary heart disease. *JAMA*. 1964;190:886.)

and cholesterol and blood pressure levels to risk of myocardial infarction and death from CHD. Recall that at this point in history, the associations of smoking and elevated levels of cholesterol and blood pressure with CHD were not yet known, although currently we all agree that they are now established risk factors for heart disease. The authors have assigned a value of 1 to the lowest of the risks in each of the two parts of the figure, and the other risks are calculated relative to this value. On the left is shown the risk in nonsmokers with low cholesterol levels (which has been set at 1) and the risk in nonsmokers with high cholesterol levels; risks for smokers with low and high cholesterol levels are each calculated relative to risks for nonsmokers with low cholesterol levels. Note that the risk is higher with high cholesterol levels, and that this holds both in smokers and in nonsmokers (although the risk is higher in smokers even when cholesterol levels are low). Thus both smoking and elevated cholesterol levels contribute to the risk of myocardial infarction and death from CHD. A comparable analysis with blood pressure and smoking is shown on the right side of the figure.

ODDS RATIO (RELATIVE ODDS)

We have seen that, to calculate a relative risk, we must have values for the incidence of the disease in the exposed and the incidence in the unexposed, as can be obtained from a cohort study. However, in a *case-control* study, we do not know the incidence in the exposed population or the incidence in the unexposed population because we start with diseased people (cases) and non-diseased people (controls). Hence, in a case-control study we *cannot* calculate the relative risk directly. In this section we will see how another measure of association, the *odds ratio* (OR), can be obtained from either a cohort or a case-control study and can be used instead of the relative risk. We will also see that even though we cannot calculate a relative risk from a case-control study, under many conditions we can obtain a very good *estimate* of the relative risk from a case-control study using the odds ratio.

Defining the Odds Ratio in Cohort and in Case-Control Studies

In previous chapters we discussed the *proportion* of the exposed population in whom disease develops and the *proportion* of the unexposed population in whom disease develops in a cohort study. Similarly, in case-control studies, we have discussed the *proportion* of the cases who were exposed and the *proportion* of the controls who were exposed (Table 12.8).

An alternate approach is to use the concept of *odds*. When betting at the racetrack, you typically consider the odds of each horse winning—the so-called handicapping system. Suppose we are betting on a horse named Epi Beauty, which has a 60% probability of

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TABLE 12.8 Calculation of Proportions Exposed in a Case-Control Study

		First, Select: *Cases (with Disease)*	First, Select: *Controls (without Disease)*
Then Measure Past Exposure	Were exposed	a	b
	Were not exposed	c	d
	Totals	$a+c$	$b+d$
	Proportions exposed	$\frac{a}{a+c}$	$\frac{b}{b+d}$

winning the race *(P)*. Epi Beauty therefore has a 40% probability of losing $(1 - P)$. If these are the probabilities, what are the *odds* that the horse will win the race? To answer this, we must keep in mind that *the odds of an event can be defined as the ratio of the number of ways the event can occur to the number of ways the event cannot occur.* Consequently, the odds of Epi Beauty winning, as defined previously, are as follows:

$$\text{Odds} = \frac{\text{Probability that Epi Beauty will win the race}}{\text{Probability that Epi Beauty will lose the race}}$$

Recall that, if P is the probability that Epi Beauty will win the race, $1 - P$ equals the probability that Epi Beauty will lose the race. Consequently, the odds of Epi Beauty winning are:

$$\text{Odds} = \frac{P}{1-P} \text{ or } \frac{60\%}{40\%} = 1.5{:}1 = 1.5$$

It is important to keep in mind the distinction between *probability* and *odds*. In the previous example:

$$\text{Probability of winning} = 60\%$$

and

$$\text{Odds of winning} = \frac{60\%}{40\%} = 1.5$$

Odds Ratio in Cohort Studies

Let us examine how the concept of odds can be applied to both cohort and case-control studies. Let us first consider the cohort study design shown in Fig. 12.5A. Our first question is, "What is the *probability (P)* that the disease will develop in an exposed person?" The answer to this is the incidence of the disease in the top row (exposed persons), which equals $\frac{a}{a+b}$. Next let us ask, "What are the *odds* that the disease will develop in an exposed person?" Again, looking only at the top row in Fig. 12.5A, we see that there are $(a + b)$ exposed persons; the odds that the disease will develop in them are $a : b$, or $\frac{a}{b}$. (Recall $\frac{P}{1+P}$ from the Epi Beauty example.) Similarly, looking only at the bottom row of this table, there are $(c + d)$ unexposed persons; the probability that the disease will develop in unexposed persons is $\frac{c}{c+d}$ and the odds of the disease developing in these unexposed persons are $c : d$, or $\frac{c}{d}$.

Just as the ratio of the incidence in the exposed to the incidence in the unexposed can be used to measure an association of exposure and disease, we can also look at

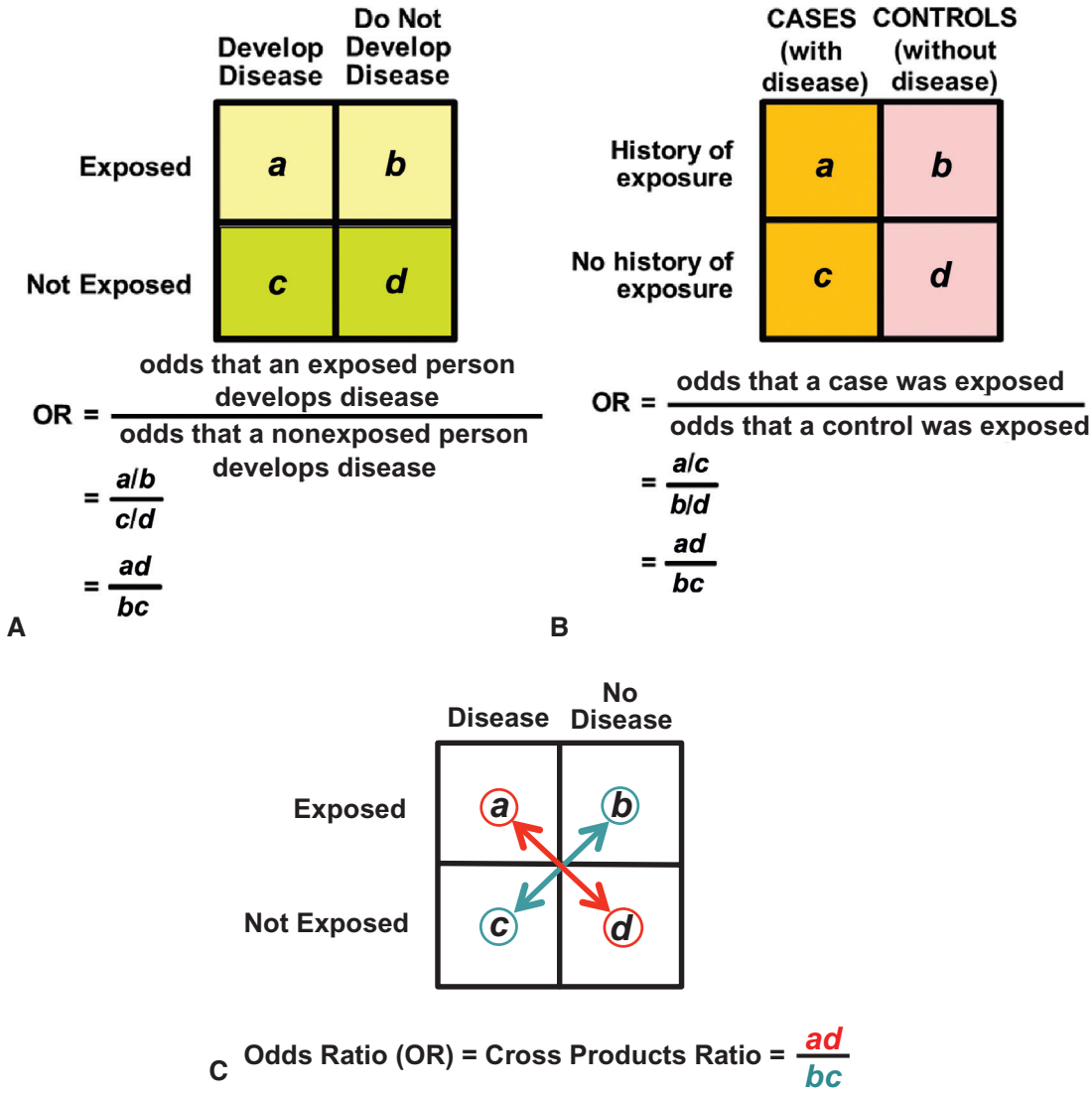

Fig. 12.5 **(A)** Odds ratio (OR) in a cohort study. **(B)** OR in a case-control study. **(C)** Cross-products ratio in both a cohort and a case-control study.

the ratio of the odds that the disease will develop in an exposed person to the odds that it will develop in an unexposed person. Either measure of association is valid in a cohort study.

In a cohort study, to answer the question of whether there is an association between the exposure and the disease, we can either use the relative risk (also called *risk ratio*) discussed in the previous section or we can use the odds ratio (also called the *relative odds*). In a *cohort study* the odds ratio is defined as the *ratio of the odds of developing disease in exposed persons to the odds of developing disease in unexposed persons*, and it can be calculated as follows:

$$\frac{\left(\frac{a}{b}\right)}{\left(\frac{c}{d}\right)} = \frac{ad}{bc}$$

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Odds Ratio in a Case-Control Study

As just discussed, in a *case-control study*, we cannot calculate the relative risk directly to determine whether there is an association between the exposure and the disease. This is because, having started with cases and controls rather than with exposed and unexposed persons, we do not have information about the incidence of disease in exposed versus unexposed persons. However, although we can use the odds ratio as a measure of the association between exposure and disease in a case-control study, we ask somewhat different questions: "What are the odds that a case was exposed?" Looking at the left-hand column in Fig. 12.5B, we see that the *odds* of a case having been exposed are $a : c$, or $\frac{a}{c}$. Next, we ask, "What are the odds that a control was exposed?" Looking at the right-hand column, we see that the *odds* of a control having been exposed are $b : d$, or $\frac{b}{d}$.

We can then calculate the odds ratio, which, in a case-control study, is defined as the ratio of the odds that the cases were exposed to the odds to which the controls were exposed. This is calculated as follows:

$$\frac{\left(\frac{a}{c}\right)}{\left(\frac{b}{d}\right)} = \frac{ad}{bc}$$

Thus, interestingly, $\frac{ad}{bc}$ represents the odds ratio (or relative odds) in *both* cohort (see Fig. 12.5A) and case-control (see Fig. 12.5B) studies. In both types of studies, the odds ratio is an excellent measure of whether a certain exposure is associated with a specific disease. The *odds ratio* is also known as the *cross-products ratio*, because it can be obtained by multiplying both diagonal cells in a 2×2 table and then dividing $\frac{ad}{bc}$, as seen in Fig. 12.5C. Note that, when calculating the odds ratio as a cross-products ratio, the format of the table must be exactly as shown in Table 12.5 (i.e., cases on the left hand side column and exposed individuals in the upper row). Failure to do so will result in an incorrectly calculated odds ratio.

Note also that, in both cohort and case-control studies, the odds ratio can be calculated as the cross-products ratio, which means that the odds ratio of exposure from a case-control study equals the odds ratio of disease. For example, in a case-control study of Alzheimer disease, a condition that is fairly common in the elderly, Tolppanen et al.,[1] using a 5-year lag time, found that cases had an odds of past brain injury 1.23 times higher than that in controls. When reporting these results, it would be correct but not too useful to say that the odds of past brain injury (exposure) in cases was 1.23 times greater than that in controls. However, because epidemiology is always concerned with identifying predictors of disease and as the odds ratio of exposure is the same as the odds ratio of disease, a more useful description of this result would be that the odds of developing Alzheimer disease in individuals with a brain injury (exposure) was 1.23 times higher than in those without an episode of brain injury. In other words, even in case-control studies, the interpretation of the odds ratio is always prospective. (Note that, because Alzheimer disease is common in the elderly, the odds ratio in this example is generally not considered to be a good estimate of the relative risk and thus the odds ratio must be described in terms of odds, not of risks. (See also the section below, titled "When Is the Odds Ratio a Good Estimate of the Relative Risk?")

The odds ratio or the cross-products ratio can be viewed as the ratio of the product of the two cells that support the hypothesis of an association (cells *a* and *d*—diseased people who were exposed and non-diseased people who were not exposed), to the product of the two cells that negate the hypothesis of an association (cells *b* and *c*—non-diseased people who were exposed and diseased people who were not exposed).

Interpreting the Odds Ratio

We interpret the odds ratio just as we have interpreted the relative risk. If the exposure is not related to the disease, the odds ratio will equal 1. If the exposure is positively related to the disease, the odds ratio will be greater than 1. If the exposure is negatively related to the disease (i.e., it is protective), the odds ratio will be less than 1.

When Is the Odds Ratio a Good Estimate of the Relative Risk?

In a case-control study, only the odds ratio can be calculated as a measure of association, whereas in a

cohort study, either the relative risk or the odds ratio is a valid measure of association. However, many people are more comfortable using the relative risk, and this is the more frequently used measure of association reported in the literature when cohort studies are published. Even when the odds ratio is used, people are often interested in knowing how well it approximates the relative risk. Even prestigious clinical journals have been known to publish reports of case-control studies and to label a column of results as *relative risks*. Having read the discussion in this chapter, you should now be aghast to see such a presentation because you now know that relative risks cannot be calculated directly from a case-control study! Clearly, what is meant is an *estimate* of relative risks based on the odds ratios that are obtained in the case-control studies.

When is the odds ratio (relative odds) obtained in a case-control study a good approximation of the relative risk in the population? When the following three conditions are met:

1. When the *cases* studied are representative, with regard to history of exposure, of all people with the disease in the population from which the cases were drawn.
2. When the *controls* studied are representative, with regard to history of exposure, of all people without the disease in the population from which the cases were drawn.
3. When the disease being studied does not occur frequently.

This third condition—also known as the "rarity assumption"—has a statistical, rather than a public health, meaning. For example, a disease with an incidence of 4% in the exposed individuals and 2% in the unexposed cannot be said to be infrequent from the population viewpoint. However, from the viewpoint of the rarity assumption, the disease is rare and thus the relative risk (2.0) and the odds ratio (2.04) are virtually the same.

The third condition (that the disease occurrence is not frequent) can be intuitively explained as follows:

Recall that there are $(a + b)$ exposed persons. Because most diseases with which we are dealing occur infrequently, very few persons in an exposed population will develop the disease; consequently, a is very small compared with b, and one can approximate $(a + b)$ as b, or $(a + b) \geqslant b$. Similarly, very few unexposed persons $(c + d)$ develop the disease, and we can approximate $(c + d)$ as d, or $(c + d) \cong d$. Therefore, we may calculate a relative risk as follows:

$$\frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)} \cong \frac{\left(\frac{a}{b}\right)}{\left(\frac{c}{d}\right)}$$

From performing this calculation, we obtain $\frac{ad}{bc}$, which is the odds ratio. For the committed reader, a neater and more sophisticated derivation is provided in the appendix to this chapter.

Figs. 12.6 and 12.7 show two examples of cohort studies that demonstrate how the odds ratio provides a good approximation of the relative risk when the occurrence of a disease is infrequent but not when it is frequent. In Fig. 12.6 the occurrence of disease is infrequent, and we see that the relative risk is 2. If we now calculate an odds (cross-products) ratio, we find it to be 2.02, which is a very close approximation.

Now, let us examine Fig. 12.7, in which the occurrence of disease is more frequent. Although the relative risk is again 2.0, the odds ratio is 3.0, which is considerably different from the relative risk.

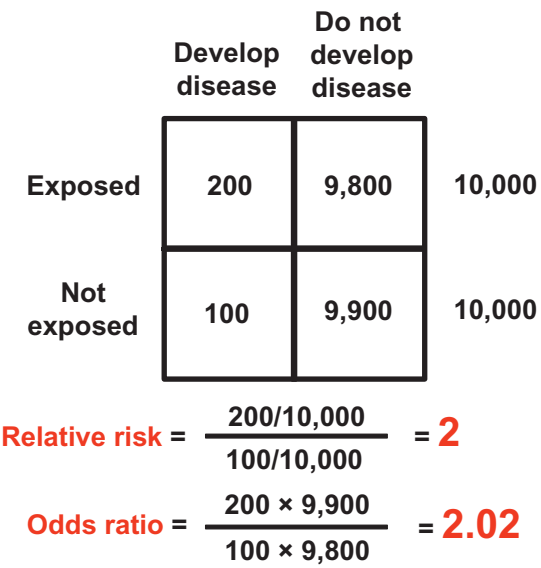

Fig. 12.6 Example: The odds ratio is a good estimate of the relative risk when a disease is infrequent.

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	Develop disease	Do not develop disease	
Exposed	50	50	100
Not exposed	25	75	100

$$\text{Relative risk} = \frac{50/100}{25/100} = 2$$

$$\text{Odds ratio} = \frac{50 \times 75}{25 \times 50} = 3$$

Fig. 12.7 Example: The odds ratio is not a good estimate of the relative risk when a disease is not infrequent.

	CASES	CONTROLS
	E	N
	E	E
	N	N
	E	N
E = Exposed	N	E
N = Not Exposed	N	N
	E	N
	E	E
	E	N
	N	N

Fig. 12.8 A case-control study of 10 cases and 10 unmatched controls.

We therefore see that the odds ratio is in itself a valid measure of association without considering relative risk. However, if you choose to use the relative risk as the index of association when the disease occurrence is infrequent, the odds ratio is a very good approximation of the relative risk.

Remember:

- The relative odds (odds ratio) is a useful measure of association, in and of itself, in both case-control and cohort studies.
- In a cohort study the relative risk can be calculated directly.
- In a case-control study the relative risk cannot be calculated directly, so that the relative odds or odds ratio (cross-products ratio) is used as an estimate of the relative risk when the risk of the disease is low.

The case-control study conducted by Arvonen et al.[2] is an example of the odds ratio as a good estimate of the relative risk. These authors found an odds ratio of 2.4 for the association of cow's milk allergy in infancy (exposure) with the development of juvenile idiopathic arthritis. Because the incidence of this disease is very low (approximately 13.9 per 100,000),[3] an accurate interpretation of the odds ratio would be that the *risk* of the disease in the exposed individuals is more than two times higher than that in the unexposed.

Examples of Calculating Odds Ratios in Case-Control Studies

In this section, we will calculate odds ratios in two case-control studies (one in which the controls were *not* matched to the cases, and the other in which they *were* matched). For purposes of these examples, let us assume the following: our research budget is incredibly small, so we have carried out a case-control study of only 10 cases and 10 controls. This disease may have just been recognized and there are very few identified cases to date; however, the disease itself is very lethal! *N* indicates an unexposed individual, and *E* indicates an *exposed* individual.

Calculating the Odds Ratio in an Unmatched Case-Control Study

Let us assume that this case-control study is done without any matching of controls to cases and that we obtain the results seen in Fig. 12.8. Thus 6 of the 10 cases were exposed and 3 of the 10 controls were exposed. If we arrange these data in a 2 × 2 table, we obtain the following:

The odds ratio in this *unmatched* study equals the ratio of the cross-products:

$$\text{Odds ratio} = \frac{ad}{bc}$$

$$\text{Odds ratio} = \frac{6 \times 7}{4 \times 3} = \frac{42}{12} = 3.5$$

TABLE 12.9 Example of Calculating an Odds Ratio from a Case-Control Study

		First, Select: *CHD Cases*	First, Select: *Controls*
Then Measure Past Exposure	Smokers	112 *(a)*	176 *(b)*
	Nonsmokers	88 *(c)*	224 *(d)*
	Totals	200 ($a + c$)	400 ($b + d$)
	Proportions smoking cigarettes	56%	44%

$$\text{Odds ratio} = \frac{ad}{bc} = \frac{112 \times 224}{176 \times 88} = 1.62$$

CHD, Coronary heart disease.

Table 12.9 shows data from an unmatched case-control study of smoking and CHD. The letters *a, b, c,* and *d* have been inserted to identify the cells of the 2 × 2 table that are used for the calculation. The odds ratio, as calculated from these data, is as follows:

$$\text{Odds ratio} = \frac{ad}{bc} = \frac{112 \times 224}{176 \times 88} = 1.62$$

Calculating the Odds Ratio in a Matched-Pairs Case-Control Study

As discussed previously, in selecting the study population in case-control studies, controls are often selected by matching each one to a case according to variables that are known to be related to disease risk, such as sex, age, or race (using individual matching or matched pairs). The results are then analyzed in terms of case-control pairs rather than for individual subjects. (Note that it is also possible to match more than one control to a case, but only matched pairs will be considered in the discussion that follows.)

What types of case-control combinations are possible in regard to exposure history? Clearly, if exposure is dichotomous (a person is either exposed or not exposed), only the following four types of case-control pairs are possible:

Note that the case-control pairs that had the same exposure experience are termed *concordant pairs* and those with different exposure experience are termed *discordant pairs*. These possibilities are shown schematically in a 2 × 2 table. Note that unlike other 2 × 2 tables that we have examined previously, the figure in each cell represents pairs of subjects (i.e., *case-control pairs*), *not* individual subjects. Thus, the table contains *a* pairs—in which both the case and the control were exposed; *b* pairs—in which the case was exposed and the control was not; *c* pairs—in which the case was not exposed and the control was exposed; and *d* pairs—in which neither the case nor the control was exposed.

Calculation of the odds ratio in such a matched-pair study is based on the *discordant pairs* only (*b* and *c*). The concordant pairs (*a* and *d*, in which cases and controls were either both exposed or both not exposed) are ignored because they do not contribute to our knowledge of how cases and controls differ with regard to history of exposure.

The odds ratio for matched pairs is therefore the ratio of the discordant pairs (i.e., the ratio of the number of pairs in which the case was exposed and the control was not, to the number of pairs in which the control was exposed and the case was not). The odds ratio for the preceding 2 × 2 table is as follows:

$$\text{Matched pairs odds ratio} = \frac{b}{c}$$

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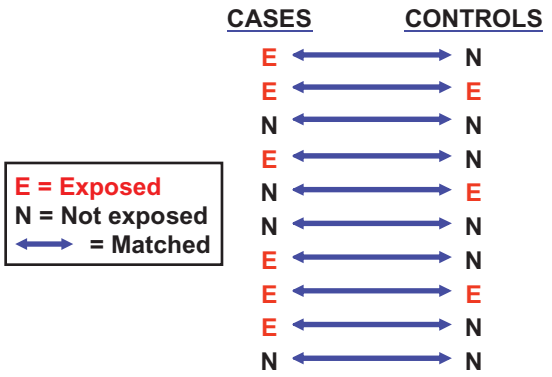

Fig. 12.9 A case-control study of 10 cases and 10 matched controls.

Again, the matched-pairs odds ratio can be viewed as the ratio of the number of pairs that support the hypothesis of an association (pairs in which the case was exposed and the control was not) to the number of pairs that negate the hypothesis of an association (pairs in which the control was exposed and the case was not).

Let us now look at an example of an odds ratio calculation in a matched-pairs case-control study (Fig. 12.9). Let us return to our low-budget study, which included only 10 cases and 10 controls: now our study is designed so that each control has been individually matched to a case, resulting in 10 case-control *pairs* (the horizontal arrows indicate the matching of pairs). If we use these findings to construct a 2 × 2 table for *pairs*, we obtain the following:

There are two pairs in which *both* the case and the control were exposed and three pairs in which *neither* the case *nor* the control was exposed. These concordant pairs are then ignored in the analysis of matched pairs.

There are four pairs in which the case was exposed and the control was not and one pair in which the control was exposed and the case was not.

Hence the odds ratio for matched pairs is as follows:

$$\text{Matched pairs odds ratio} = \frac{b}{c} = \frac{4}{1} = 4$$

Figs. 12.10 and 12.11 present data selected from the case-control study of brain tumors in children that was discussed in a previous chapter. Data are shown for two variables. Fig. 12.10 presents a matched-pairs analysis for birth weight. A number of studies have suggested that children with higher birth weights are at increased risk for certain childhood cancers. In this analysis, *exposure* is defined as birth weight greater than 8 lb. The result is an odds ratio of 2.57.

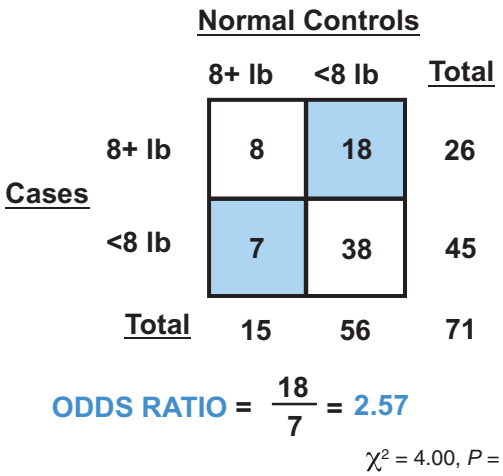

Fig. 12.10 Birth weight of index child: matched-pairs comparison of cases and normal controls (≥8 lb vs. <8 lb). (Data from Gold E, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol.* 1979;109:309–319.)

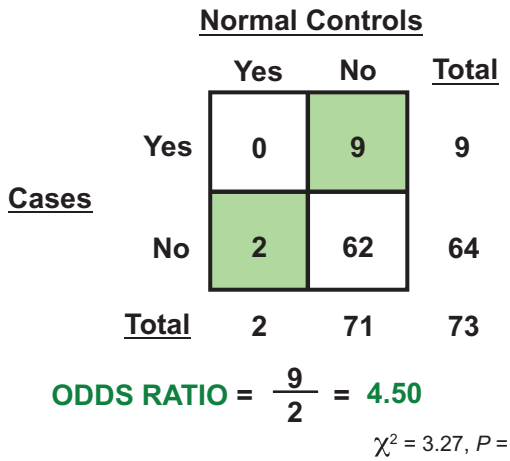

Fig. 12.11 Exposure of index child to sick pets: matched-pairs comparison of cases and normal controls. (Data from Gold E, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol.* 1979;109:309–319.)

In Fig. 12.11 a matched-pairs analysis is presented for exposure to sick pets. Many years ago, the Tri-State Leukemia Study found that more cases of leukemia than controls had family pets. Interest in oncogenic viruses stimulated an interest in exposure to sick pets as a possible source of such agents. Gold and coworkers explored this question in their case-control study,[4] and the

results are shown in Fig. 12.11. Although the odds ratio was 4.5, the number of discordant pairs was very small.

Although the aforementioned examples are a bit historical, the way the calculation of both RR and OR is done is the same in more contemporary research articles. However, the current presentation of the results focuses more on adjustment to potential confounding variables.

CONCLUSION

This chapter has introduced the concepts of absolute risk, relative risk, and odds ratio. In Chapter 13 we turn to another important aspect of risk: the attributable risk. We will then review the study designs and indices of risk that have been discussed before addressing the use of these concepts in deriving causal inferences.

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3. Towner SR, Michet CJ Jr, O'Fallon WM, et al. The epidemiology of juvenile arthritis in Rochester, Minnesota 1960–1979. *Arthritis Rheum.* 1983;26:1208–1213.
4. Gold E, Gordis L, Tonascia J, et al. Risk factors for brain tumors in children. *Am J Epidemiol.* 1979;109:309–319.

REVIEW QUESTIONS FOR CHAPTER 12

1. *Of 2,872 persons who had received radiation treatment in childhood because of an enlarged thymus, cancer of the thyroid developed in 24 and a benign thyroid tumor developed in 52. A comparison group consisted of 5,055 children who had received no such treatment (brothers and sisters of the children who had received radiation treatment). During the follow-up period, none of the comparison group developed thyroid cancer, but benign thyroid tumors developed in six. Calculate the relative risk for benign thyroid tumors:* _____

Questions 2 and 3 are based on the information given in the following table.

In a small pilot study, 12 women with uterine cancer and 12 with no apparent disease were contacted and asked whether they had ever used estrogen. Each woman with cancer was matched by age, race, weight, and parity to a woman without disease. The results are shown below:

Pair No.	Women With Uterine Cancer	Women Without Uterine Cancer
1	Estrogen user	Estrogen nonuser
2	Estrogen nonuser	Estrogen nonuser
3	Estrogen user	Estrogen user
4	Estrogen user	Estrogen user
5	Estrogen user	Estrogen nonuser
6	Estrogen nonuser	Estrogen nonuser
7	Estrogen user	Estrogen nonuser
8	Estrogen user	Estrogen nonuser
9	Estrogen nonuser	Estrogen user
10	Estrogen nonuser	Estrogen user
11	Estrogen user	Estrogen nonuser
12	Estrogen user	Estrogen nonuser

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2. *What is the estimated relative risk of cancer when analyzing this study as a matched-pairs study?*
   a. 0.25
   b. 0.33
   c. 1.00
   d. 3.00
   e. 4.20
3. *Unmatch the pairs. What is the estimated relative risk of cancer when analyzing this study as an unmatched study design?*
   a. 0.70
   b. 1.43
   c. 2.80
   d. 3.00
   e. 4.00
4. *In a study of a disease in which all cases that developed were ascertained, if the relative risk for the association between a factor and the disease is equal to or less than 1.0, then:*
   a. There is no association between the factor and the disease
   b. The factor protects against development of the disease
   c. Either matching or randomization has been unsuccessful
   d. The comparison group used was unsuitable, and a valid comparison is not possible
   e. There is either no association or a negative association between the factor and the disease

Questions 5 through 7 are based on the following information.

Talbot and colleagues carried out a study of sudden unexpected death in women. Data on smoking history are shown in the following table.

Smoking History for Cases of Atherosclerotic Heart Disease Sudden Death and Controls (Current Smoker, 1+ Pack/Day) [Matched Pairs], Allegheny County, 1980

	Controls		
Cases	Smoking 1+ Pack/Day	Smoking <1 Pack/Day	Totals
Smoking 1+ pack/day	2	36	38
Smoking <1 pack/day	8	34	42
Totals	10	70	80

(Modified from Talbott E, Kuller LH, Perper J, Murphy PA. Sudden unexpected death in women: biologic and psychosocial origins. *Am J Epidemiol.* 1981;114:671–682.)

5. *Calculate the matched-pairs odds ratio for these data.* _____
6. *Using data from the table, unmatch the pairs and calculate an unmatched odds ratio.* _____
7. *What are the odds that the controls smoke 1+ pack/day?* _____

Questions 8 and 9 are based on the information given in the following table.

Rates of Atherosclerotic Heart Disease (ASHD) per 10,000 Population, by Age and Sex, Framingham, Massachusetts

Age at Beginning of Study (year)	MEN: ASHD Rates at Initial Exam	MEN: Yearly Follow-up Exams (Mean Annual Incidence)	WOMEN: ASHD Rates at Initial Exam	WOMEN: Yearly Follow-up Exams (Mean Annual Incidence)
29–34	76.7	19.4	0.0	0.0
35–44	90.7	40.0	17.2	2.1
45–54	167.6	106.5	111.1	29.4
55–62	505.4	209.1	211.1	117.8

8. *The relative risk for developing ASHD subsequent to entering this study in men as compared with women is:*
- **a.** Approximately equal in all age groups
- **b.** Highest in the oldest age group
- **c.** Lowest in the youngest and oldest age groups, and highest at ages 35 to 44 and 45 to 54 years
- **d.** Highest in the youngest and oldest age groups, and lowest at ages 35 to 44 and 45 to 54 years
- **e.** Lowest in the oldest age group

9. *The most likely explanation for the differences in rates of ASHD between the initial examination and the yearly follow-up examinations in men is:*
- **a.** The prevalence and incidence of ASHD increase with age in men
- **b.** Case-fatality of ASHD is higher at younger ages in men
- **c.** A classic cohort effect explains these results
- **d.** The case-fatality in ASHD is highest in the first 24 hours following a heart attack
- **e.** The initial examination measures the prevalence of ASHD, whereas the subsequent examinations primarily measure the incidence of ASHD

Question 10 is based on the following information.

A matched case-control study is conducted to explore the relationship of C-reactive protein (CRP) and progression to AIDS in South Africa. Each case is matched to one control; they are selected from separate HIV-care clinics from the United States. The cases and controls are matched by age and sex, which are known confounders of the relationship between CRP and progression to AIDS. The exposure was a high CRP value, defined as ≥2 mg/L. The following distribution of exposure was observed among 145 case-control pairs.

		CONTROL: +	CONTROL: −
Case	+	25	31
	−	16	73

10. *Calculate the odds ratio (OR) for the case-control study*
OR = _____

Questions 11 and 12 involve a case-control study exploring the relationship between use of aspirin and odds of prostate cancer in a study with 375 cases and 407 controls.

Aspirin Use	Case	Control
Never	198	174
Ever	177	233

11. *What is the odds ratio for prostate cancer comparing never versus ever aspirin?* (Ever use *is the reference category).*

_____

12. *Provide a one-sentence interpretation of the odds ratio you obtained in Question 11:*

13. *Which of the following generally cannot be estimated in a case-control study?*
- **a.** Relative risk
- **b.** Incidence rate
- **c.** Prevalence of exposure in the source population
- **d.** Odds ratio of disease
- **e.** Odds ratio of exposure

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APPENDIX TO CHAPTER 12

Derivation of the relationship of the odds ratio and the relative risk can be demonstrated by the following algebra. Recall that:

$$\text{Relative risk (RR)} = \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)}$$

$$\text{The odds ratio (OR)} = \frac{ad}{bc}$$

The relationship of the relative risk to the odds ratio can therefore be expressed as the ratio of the RR to the OR:

(1) Formula 1:

$$\frac{\text{RR}}{\text{OR}} = \frac{\left(\frac{a}{a+b}\right) \div \left(\frac{c}{c+d}\right)}{\left(\frac{ad}{bc}\right)}$$

$$= \frac{\left(\frac{a}{a+b}\right)}{\left(\frac{c}{c+d}\right)} \times \frac{bc}{ad}$$

$$= \frac{\left(\frac{abc}{a+b}\right)}{\left(\frac{cad}{c+d}\right)} = \frac{\left(\frac{b}{a+b}\right)}{\frac{d}{c+d}}$$

Since

$$\frac{b}{a+b} = \frac{a+b-a}{a+b} = \frac{a+b}{a+b} = \frac{a}{a+b} = 1 - \frac{a}{a+b}$$

and

$$\frac{d}{c+d} = \frac{c+d-c}{c+d} = \frac{c+d}{c+d} = \frac{c}{c+d} = 1 - \frac{c}{c+d}$$

the relationship of the relative risk to the odds ratio can therefore be reduced to the following equation:

(2) Formula 2:

$$\frac{\text{RR}}{\text{OR}} = \frac{1 - \left(\frac{a}{a+b}\right)}{1 - \left(\frac{c}{c+d}\right)}$$

If we then multiply Formula 2 by the OR:

(3) Formula 3:

$$\text{RR} = \frac{1 - \left(\frac{a}{a+b}\right)}{1 - \left(\frac{c}{c+d}\right)} \times \text{OR}$$

If a disease is rare, both $\frac{a}{a+b}$ and $\frac{c}{c+d}$ will be very small, so that the terms in parentheses in Formula 3 will be approximately 1, and the odds ratio will then approximate the relative risk.

It also is of interest to examine this relationship in a different form. Recall the definition of *odds* (i.e., the ratio of the number of ways the event can occur to the number of ways the event cannot occur):

$$O = \frac{P}{1-P}$$

where O is the *odds* that the disease will develop and P is the *risk* that the disease will develop. Note that, as P becomes smaller, the denominator $1 - P$ approaches 1, with the result that:

$$\frac{P}{1-P} \cong \frac{P}{1} = P$$

(i.e., the *odds* become a good approximation of the *risk*). Thus, if the risk is low (the disease is rare), the *odds* that the disease will develop are a good approximation of the *risk* that it will develop.

Now, consider an exposed group and an unexposed group. If the risk of a disease is very low, the *ratio* of the *odds* in the exposed group to the *odds* in the unexposed group closely approximates the *ratio* of the *risk* in the exposed group to the *risk* in the unexposed group *(the relative risk)*.

That is, when P is very small:

$$\frac{O_{exp}}{O_{nonexp}} \cong \frac{P_{exp}}{P_{nonexp}}$$

where:

O_{exp} is the odds of the disease developing in the exposed population,

O_{nonexp} is the odds of the disease developing in the unexposed population,

P_{exp} is the probability (or risk) of the disease developing in the exposed population, and

P_{nonexp} is the probability (or risk) of the disease developing in the unexposed population.

This ratio of odds is the *odds ratio* (relative odds).

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13

More on Risk: Estimating the Potential for Prevention

LEARNING OBJECTIVES

- To calculate and interpret the attributable risk for the exposed group.
- To calculate and interpret the population attributable risk.
- To describe how attributable risk is used to estimate the potential for prevention.

ATTRIBUTABLE RISK

Our discussion in Chapter 12 addressed the relative risk and the odds ratio, which is often used as a surrogate for the relative risk in a case-control study. The *relative risk* is an important measure of the *direction and strength (or magnitude) of the association*, which is a major consideration in deriving causal inferences. In this chapter, we turn to a different question: *How much of the disease that occurs can be attributed to a certain exposure?* This is answered by another measure of risk, the *attributable risk*, which is defined as the amount or proportion of disease incidence (or disease risk) that can be attributed to a specific exposure. For example, how much of the coronary heart disease (CHD) risk experienced by smokers can be attributed to smoking? How much can be attributed to host genetics? Whereas the relative risk is important in establishing etiologic relationships, the attributable risk is in many ways more important in clinical practice and in public health, because it addresses a different question: *How much of the risk (incidence) of disease can we hope to prevent if we are able to eliminate exposure to the agent in question?*

We can calculate the attributable risk for exposed persons (e.g., the attributable risk of CHD in smokers) or the attributable risk for the total population, which includes both exposed and unexposed persons (e.g., the attributable risk of CHD in a total population, which consists of both smokers and nonsmokers). These calculations and their uses and interpretations are discussed in this chapter.

Attributable Risk for the Exposed Group

Fig. 13.1 offers a schematic introduction to this concept. Consider two groups: one exposed and the other not exposed. In Fig. 13.1A, the total risk of the disease in the exposed group is indicated by the full height of the bar on the left, and the total risk of disease in the unexposed group is indicated by the full height of the bar on the right. As seen here, the total risk of the disease is higher in the exposed group than in the unexposed group. We can ask the following question: *In the exposed persons, how much of the total risk of disease is actually due to exposure* (e.g., in a group of smokers, how much of the risk of CHD is due to smoking)?

How can this question be answered? Let's start by addressing the unexposed persons, designated by the bar on the right. Although they are not exposed, they have some risk of disease (albeit at a lower level than that of the exposed persons). That is, the risk of the disease is not zero even in unexposed persons. For instance, in this example of smoking and CHD, nonsmokers may have some risks of CHD, possibly due to obesity, elevated blood pressure and cholesterol levels, among other factors. This risk is

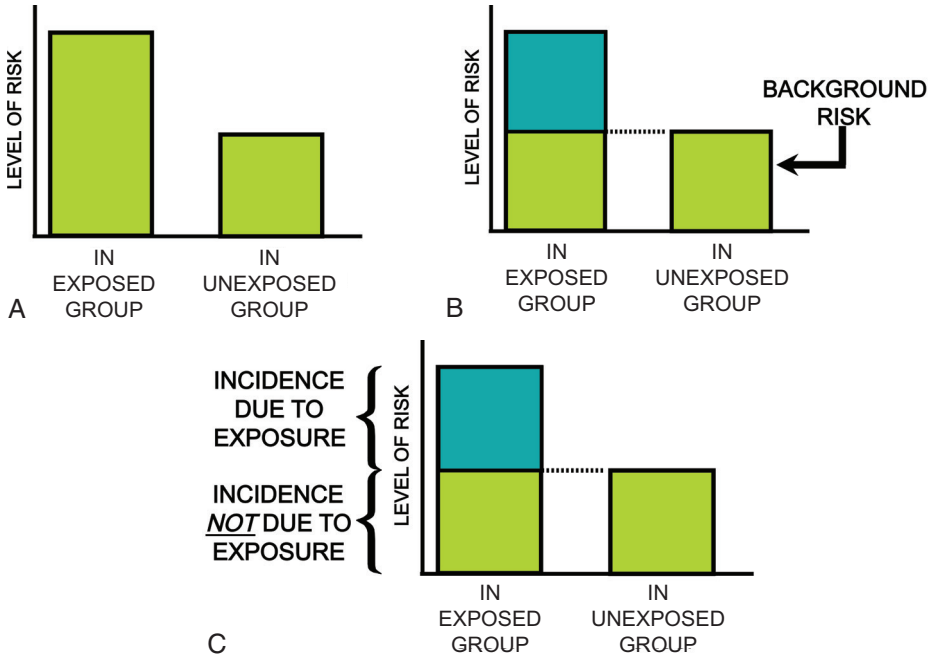

Fig. 13.1 **(A)** Total risks in exposed and unexposed groups. **(B)** Background risk. **(C)** Incidence attributable to exposure and incidence not attributable to exposure.

termed *background (residual) risk*. Every person shares the background risk regardless of whether or not he or she has had the specific exposure in question (in this case, tobacco smoking; see Fig. 13.1B). Thus, both unexposed and exposed persons have this background risk. Therefore, the total risk of the disease in exposed individuals is the sum of the background risk that any person has and the additional risk due to the exposure in question (e.g., smoking). If we want to know how much of the total risk in exposed persons is due to the exposure, we should subtract the background risk from the total risk (see Fig. 13.1C). Because the risk in the unexposed group is equal to the background risk, we can calculate the risk in the exposed group that is a result of the specific exposure by subtracting the risk in the unexposed group (the background risk) from the total risk in the exposed group.

Thus, the incidence of a disease that is attributable to the exposure in the exposed group can be calculated as follows:

Formula 13.1

$$\left(\begin{array}{c}\text{Incidence in}\\ \text{exposed group}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)$$

We could instead ask, "What proportion of the risk in exposed persons is due to the exposure?" We could then express the attributable risk as the proportion of the total incidence in the exposed group that is attributable to the exposure by simply dividing Formula 13.1 by the incidence in the exposed group, as follows:

Formula 13.2

$$\frac{\left(\begin{array}{c}\text{Incidence in}\\ \text{exposed group}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)}{\text{Incidence in exposed group}}$$

The attributable risk expresses the most that we can hope to accomplish in reducing the risk of the disease if we eliminate the exposure. For example, if all smokers were induced to stop smoking, how much of a reduction could we anticipate in the CHD rates in the future? From a practical programmatic standpoint, the attributable risk may be more relevant than the relative risk. The relative risk is a measure of the strength of the association, but the attributable risk indicates the potential for prevention if the exposure could be eliminated.

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The practicing clinician is mainly interested in the attributable risk in the exposed group: For example, when a physician advises a patient to stop smoking, they are in effect telling the patient that stopping smoking will reduce the risk of CHD. Implicit in this advice is the physician's estimate that the patient's risk will be reduced by a certain proportion if they stop smoking; the risk reduction is motivating the physician to give that advice. Although the physician often does not have a specific value in mind for the attributable risk, they are in effect relying on an attributable risk for an exposed group (smokers) to which the patient belongs. The physician is implicitly addressing the question: In a population of smokers, how much of the CHD that they experience is due to smoking, and consequently, how much of the CHD could be prevented if they did not smoke? Thus, attributable risk tells us the potential for prevention.

If all the incidence of a disease were the result of a single factor, the attributable risk for that disease would be 100%. However, this is rarely if ever the case. Both the concept and the calculation of attributable risk imply that not all disease incidence is due to a single specific exposure, as the disease even develops in some unexposed individuals. Fig. 13.2 recapitulates this concept.

Attributable Risk for the Total Population—Population Attributable Risk

Let's turn to a somewhat different question relating to attributable risk. Assume that we know how to eliminate smoking. We tell the mayor that we have a highly effective way to eliminate smoking in the community, and we want her to provide the funds to support such a program. The mayor responds that she is delighted to hear the news, but asks, "What will the impact of your smoking cessation program be on coronary heart disease incidence rates in our city?" This question differs from that which was just discussed. If we talk about CHD rates in the entire population of a city, and not just in exposed individuals, we are talking about a population that is composed of both smokers and nonsmokers. The mayor is not asking what impact we will have on smokers in this city, but rather what impact will we have on the entire population of the city, which includes both smokers and nonsmokers.

Let's consider this question further. In addition to the assumption that we have an evidence-based successful smoking cessation program, let's also assume that everyone in the city smokes. (Heaven forbid!) We now want to calculate the attributable risk. Clearly, because everyone in the city smokes, the attributable risk for the entire population of the city would equal the attributable risk for the exposed population. If everybody smokes, the attributable risk for the exposed group tells us what we can hope to accomplish with a smoking cessation program in the total population.

Now let's assume that an ideal situation exists and that nobody in the city smokes. What will be the potential for preventing CHD through the use of a completely effective smoking cessation program that we wish to apply to the population of the city? The answer is zero; because there are no exposed people in the city, a program that aims at eliminating the exposure does not make sense and would therefore have no effect on the risk of CHD. Therefore the spectrum of potential effect runs from a maximum (if everybody smokes) to zero (if nobody smokes). Of course, in reality, the answer is generally somewhere in between, because some members of the population smoke and most do not. The latter group (all nonsmokers) clearly will not benefit from a smoking cessation program, regardless of how effective it is.

To this point, we have discussed the concept and calculation of attributable risk for *an exposed group.* For example, in a population of smokers, how much of

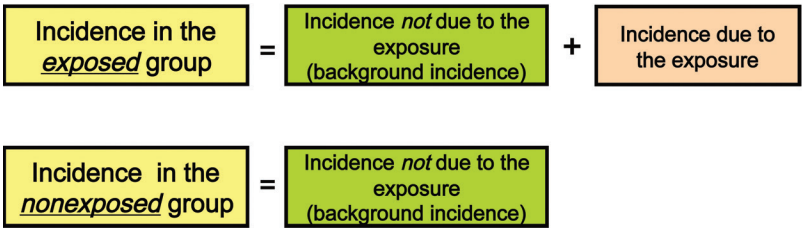

Fig. 13.2 The concept of attributable risk.

the CHD that they experience is due to smoking, and consequently, how much of the CHD could be prevented if they did not smoke? However, to answer the mayor's question as to what effect the smoking cessation program will have on the city's population as a whole, we need to calculate the *attributable risk for the total population:* What proportion of the disease incidence in a *total population* (including both exposed and unexposed people) can be attributed to a specific exposure? What would be the total impact of a prevention program on the community? If we want to calculate the attributable risk in the total population, the calculation is similar to that for exposed people, but we begin with the *incidence in the total population* and again subtract the background risk, or the incidence in the unexposed population. The incidence in the total population that is due to the exposure[a] can be calculated as shown in Formula 13.3:

Formula 13.3

$$\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\\ \text{(background risk)}\end{array}\right)$$

Again, if we prefer to express this as the proportion of the incidence in the total population that is attributable to the exposure, Formula 13.3 can be divided by the incidence in the total population:

Formula 13.4

$$\frac{\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)}{\text{Incidence in total population}}$$

The attributable risk for the total population (population attributable risk [PAR]) is a valuable concept for the public health worker. The question addressed is: What proportion of CHD in the total population can be attributed to smoking? This question could be reworded as follows: If smoking were eliminated, what proportion of the incidence of CHD in the total population (which consists of both smokers and nonsmokers) would be prevented? The answer is: the attributable risk in the total population—or the PAR (as discussed earlier).[b]

From a public health standpoint, this is often both the critical issue and the question that is raised by policy makers and by those responsible for funding prevention programs. They may want to know what the proposed program is going to do for the community as a whole. How is it going to change the burden on the health care system or the burden of suffering in the entire community, not just in exposed individuals? For example, if all smokers in the community stopped smoking, what would be the impact of this change on the incidence of CHD in the total population of the community (which includes both smokers and nonsmokers)?

An Example of an Attributable Risk Calculation for the Exposed Group

Here we present a step-by-step calculation of the attributable risk in both an exposed group and in a total population. We will use the hypothetical example previously presented of a cohort study of smoking and CHD. The data are again shown in Table 13.1.

The incidence of CHD in the exposed group (smokers) that is attributable to the exposure is calculated using Formula 13.1:

Formula 13.1

$$\left(\begin{array}{c}\text{Incidence in}\\ \text{exposed group}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right) = \frac{28.0 - 17.4}{1{,}000} = \frac{10.6}{1{,}000}$$

What does this mean? It means that 10.6 of the 28/1,000 incident cases in smokers are attributable to the fact that these people smoke. Stated another way, if we had an

[a]The incidence in the population that is due to the exposure can also be calculated as follows: Attributable risk for the exposed group × Proportion of the population exposed.

[b]Another way to calculate the attributable risk for the total population is to use Levin's formula, which is given in the appendix to this chapter. Levin's formula allows the estimation of the PAR using case-control data by replacing the relative risk with the odds ratio (if the disease is relatively rare). It requires, however, an estimate of the prevalence of the exposure in the reference population. Note that Levin's formula only applies to PARs based on unadjusted relative risks.

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TABLE 13.1 Smoking and Coronary Heart Disease (CHD): A Hypothetical Cohort Study of 3,000 Cigarette Smokers and 5,000 Nonsmokers

	CHD Develops	CHD Does Not Develop	Total	Incidence Per 1,000 Per Year
Smoke cigarettes	84	2,916	3,000	28.0
Do not smoke cigarettes	87	4,913	5,000	17.4

$$\text{Incidence among smokers} = \frac{84}{3{,}000} = 28.0 \text{ per } 1{,}000$$

$$\text{Incidence among nonsmokers} = \frac{84}{5{,}000} = 17.4 \text{ per } 1{,}000$$

effective smoking cessation campaign, we could hope to prevent 10.6 of the $\frac{28}{1{,}000}$ incident cases of CHD that smokers experience.

If we prefer, we can express this as a proportion. The proportion of the total incidence in the exposed group that is attributable to the exposure can be calculated by dividing Formula 13.1 by the incidence in the exposed group (Formula 13.2):

Formula 13.2

$$\frac{\left(\begin{array}{c}\text{Incidence in}\\ \text{exposed group}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)}{\text{Incidence in exposed group}} = \frac{28.0 - 17.4}{28.0} = \frac{10.6}{28.0} = 0.379 = 37.9\%$$

Thus 37.9% of the incidence from CHD among smokers may be attributable to smoking and could presumably be prevented by eliminating smoking.

An Example of an Attributable Risk Calculation in the Total Population (Population Attributable Risk)

Using the same example, let's calculate the PAR—that is, the attributable risk for the total population. The question we are asking is: What can we hope to accomplish with our smoking cessation program *in the total population* (i.e., the entire community, which consists of both smokers and nonsmokers)?

Remember that in the total population, the incidence that is due to smoking (the exposure) can be calculated by subtracting the background risk (i.e., the incidence in the nonsmokers, or unexposed) from the incidence in the total population:

Formula 13.3

$$\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right) - \left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)$$

To calculate Formula 13.3, we must know either the incidence of the disease (CHD) in the total population (which we often do not know) or all of the following three values, from which we can then calculate the incidence in the total population:

1. The incidence among smokers
2. The incidence among nonsmokers
3. The proportion of the total population that smokes

In this example, we know that the incidence among the smokers is 28.0 per 1,000 and the incidence among the nonsmokers is 17.4 per 1,000. However, we do not know the incidence in the total population. Let's assume that, from some other source of information, we know that the proportion of smokers in the population is 44% (and therefore the proportion of nonsmokers is 56%). The incidence in the total population can then be calculated as follows:

$$\left(\begin{array}{c}\text{Incidence}\\ \text{in smokers}\end{array}\right)\left(\begin{array}{c}\%\text{ Smokers}\\ \text{in population}\end{array}\right) + \left(\begin{array}{c}\text{Incidence in}\\ \text{nonsmokers}\end{array}\right)\left(\begin{array}{c}\%\text{ Nonsmokers}\\ \text{in population}\end{array}\right)$$

(We are simply weighting the calculation of the incidence in the total population, taking into account

the proportion of the population that smokes and the proportion of the population that does not smoke.)

So, in this example, the incidence in the total population can be calculated as follows:

$$\left(\frac{28.0}{1{,}000}\right)(0.44)+\left(\frac{17.4}{1{,}000}\right)(0.56)=\frac{22.1}{1{,}000}$$

We now have the values needed for using Formula 13.3 to calculate the attributable risk in the total population:

Formula 13.3

$$\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right)-\left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)$$
$$=\frac{22.1}{1{,}000}-\frac{17.4}{1{,}000}=\frac{4.7}{1{,}000}$$

What does this tell us? How much of the total risk of CHD in this population (which consists of both smokers and nonsmokers) is attributable to smoking? If we had an effective prevention program (smoking cessation) in this population, how much of a reduction in CHD incidence could we anticipate, at best, in the total population (of both smokers and nonsmokers)?

If we prefer to calculate the proportion of the incidence in the total population that is attributable to the exposure, we can do so by dividing Formula 13.3 by the incidence in the total population, as in Formula 13.4:

Formula 13.4

$$\frac{\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right)-\left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)}{\text{Incidence in total population}}$$
$$=\frac{22.1-17.4}{22.1}=21.3\%$$

Thus 21.3% of the incidence of CHD in the total population can be attributed to smoking, and if an effective prevention program eliminated smoking, the best that we could hope to achieve would be a reduction of 21.3% in the incidence of CHD in the total population (which includes both smokers and nonsmokers).

Attributable risk is a critical concept in virtually any area of public health and in clinical practice as well, in particular in relation to questions regarding the potential of preventive measures. For example, Lim and colleagues[1] estimated the actual causes of death worldwide in 2010. These estimates used published data and applied attributable risk calculations, as well as other approaches. Their estimates are shown in Fig. 13.3. The authors reported that dietary risk factors and physical inactivity accounted for 30% of all deaths.

It is also of interest that in the legal arena, in which toxic tort litigation has become increasingly common, the concept of attributable risk for the exposed individuals has taken on great importance. One of the legal criteria used in finding a company responsible for an environmental injury, for example, is whether it is "more likely than not" that the company caused the injury. It has been suggested that an attributable risk of greater than 50% might represent a quantitative determination of the legal definition of "more likely than not."

COMPARISON OF RELATIVE RISK AND ATTRIBUTABLE RISK

In earlier chapters, we discussed several measures of risk and of excess risk. The relative risk and the odds ratio are important as measures of the strength of the association, which is a critical consideration in deriving a causal inference. The attributable risk is a measure of how much of the disease risk is attributable to a certain exposure. Consequently, the attributable risk is useful in answering the question of how much disease can be prevented if we have an effective means of eliminating the exposure in question. Thus, the attributable risk has major applications in clinical practice and public health whereas the relative risk is valuable in etiologic studies of disease.

Table 13.2 shows a classic example from a study by Doll and Peto[2] that relates mortality from lung cancer and CHD in smokers and non-smokers and provides an illuminating comparison of relative risk and attributable risk in the same set of data.

Let's first examine the data for lung cancer. (Note that in this example, we are using mortality as a surrogate for risk.) We see that the lung cancer mortality risk is 140 per 100,000 smokers and 10 per 100,000 nonsmokers. We can calculate the relative risk as $\frac{140}{10}=14$.

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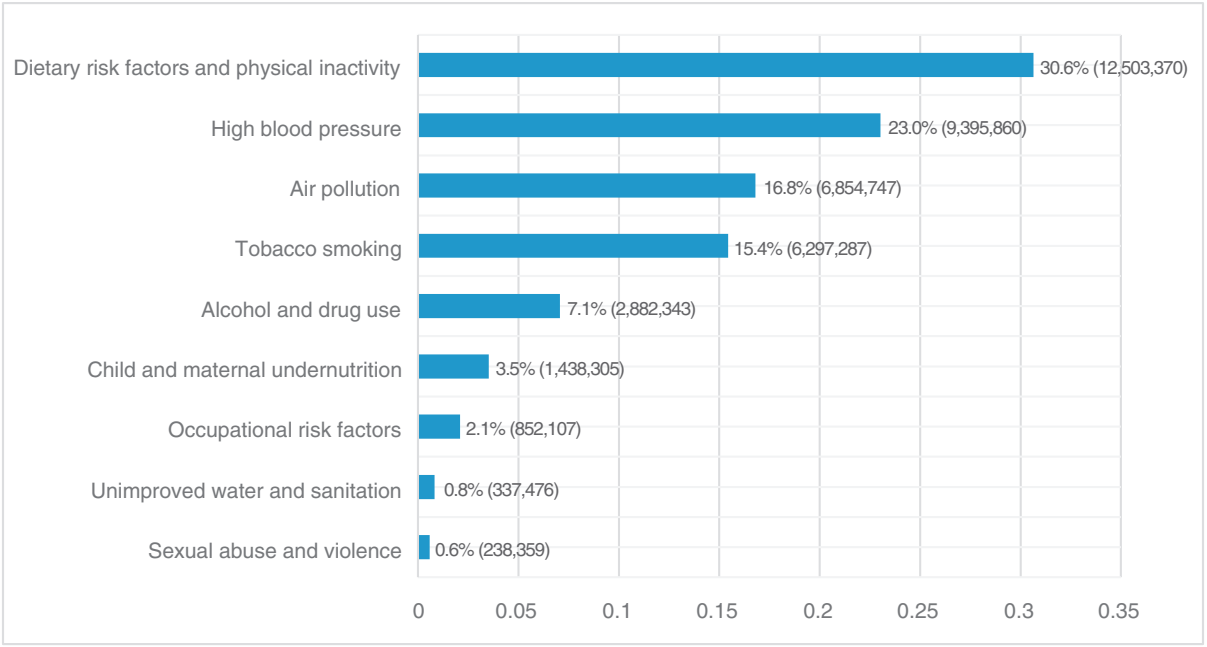

Fig. 13.3 Deaths attributable to selected risk factors or risk factor clusters in 2010, worldwide. (Data modified from Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2224–2260.)

TABLE 13.2 Lung Cancer and Coronary Heart Disease Mortality in Male British Physicians: Smokers vs. Nonsmokers

	AGE-ADJUSTED DEATH RATES PER 100,000				
	Smokers	Nonsmokers	Relative Risk	Attributable Risk (Deaths per 100,000)	% Attributable Risk
Lung cancer	140	10	14.0	130	92.9
Coronary heart disease	669	413	1.6	256	38.3

From Doll R, Peto R. Mortality in relation to smoking: twenty years' observation on male British doctors. *Br Med J.* 1976;2:1525–1536.

Now let's look at the data for CHD. The CHD mortality rate is 669 in smokers and 413 in nonsmokers. The relative risk can be calculated as $\frac{669}{413} = 1.6$. Thus, the relative risk is much higher for smoking and lung cancer than it is for smoking and CHD.

Now let's turn to the attributable risks in smokers. How much of the total risk in smokers can we attribute to smoking? To calculate the attributable risk, we subtract the background risk—the risk in the unexposed group (nonsmokers)—from the risk in the exposed group (smokers). With the data for lung cancer used, 140 − 10 = 130.

To calculate the attributable risk for CHD and smoking, we subtract the risk in the unexposed group (nonsmokers) from the risk in the exposed group (smokers), 669 − 413 = 256. That is, of the total 669 deaths per 100,000 in smokers, 256 can be attributed to smoking.

If we prefer to express the attributable risk for lung cancer and smoking as a proportion (i.e., the proportion of the lung cancer risk in smokers that can be attributed to smoking), we divide the attributable risk by the risk in smokers:

$$\frac{(140 - 10)}{140} = 92.9\%$$

If we prefer to express the attributable risk of CHD and smoking as a proportion (the proportion of the CHD risk in smokers that can be attributed to smoking), we divide the attributable risk by the risk in smokers:

$$\frac{(669 - 413)}{669} = 38.3\%$$

What do these calculations tell us? First, we see a tremendous difference in the relative risks for lung cancer and for CHD in relation to smoking: 14.0 for lung cancer compared with 1.6 for CHD (i.e., a much stronger association exists for smoking and lung cancer than for smoking and CHD). However, the attributable risk is almost twice as high (256) for CHD as it is for lung cancer (130). If we choose to express the attributable risk as a proportion, we find that 92.9% of lung cancer deaths in smokers can be attributed to smoking (and are potentially preventable by eliminating smoking), compared with only 38.3% of deaths from CHD in smokers that can be attributed to smoking.

Thus, the relative risk is much higher for lung cancer than for CHD, and the attributable risk expressed as a proportion is also much higher for lung cancer. However, if an effective smoking cessation program were available today and smoking were eliminated, would the preventive impact be greater on mortality from lung cancer or from CHD? If we examine the table, we see that if smoking were eliminated, 256 deaths per 100,000 from CHD would be prevented in contrast to only 130 from lung cancer, despite the fact that the relative risk is higher for lung cancer and despite the fact that the proportion of deaths attributable to smoking is greater for lung cancer. Why is this so? This is a result of the fact that the mortality level in smokers is much higher for CHD than for lung cancer (669 compared to 140) and that the attributable risk in those exposed to smoking (the difference between total risk in smokers and background risk) is much greater for CHD than for lung cancer. This can directly inform public health efforts and prioritization of resource allocation.

It is important to emphasize that, as the attributable risk implies that a certain proportion of the risk can be prevented, it should be estimated only when there is reasonable certainty that the association of the risk factor with the disease is causal.[3] In addition, for risk factors with a cumulative exposure, it is more appropriate to define attributable risk as the proportion of the risk (either in the exposed or in the population) that can be attributed to a given exposure than as the proportion that can be eliminated by cessation of exposure. For example, according to the US Surgeon General's Report from 2010, lung cancer risk in former smokers 15 years after quitting is one-half that in current smokers, which means that it is still considerably higher than the risk in never-smokers.

CONCLUSION

In this chapter, we have introduced the concept of attributable risk and described how it is calculated and interpreted. Attributable risk is summarized in the four calculations shown in Table 13.3.

The concepts of relative risk and attributable risk are essential for understanding causation and the potential

TABLE 13.3 Summary of Attributable Risk Calculations

	In Exposed Group	In Total Population
Incidence attributable to exposure	(Incidence in **exposed group**) − (Incidence in **unexposed group**)	(Incidence in **total population**) − (Incidence in unexposed group)
Proportion of incidence attributable to exposure	[(Incidence in **exposed group**) − (Incidence in unexposed group)] / (Incidence in **exposed group**)	[(Incidence in **total population**) − (Incidence in unexposed group)] / (Incidence in **total population**)

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for prevention. Several measures of risk have now been discussed: (1) absolute risk, (2) relative risk, (3) odds ratio, and (4) attributable risk. In Chapter 14, we will briefly review study designs and concepts of risk before proceeding to a discussion of how we use estimates of excess risk to inform causal inference.

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REVIEW QUESTIONS FOR CHAPTER 13

1. *Several studies have found that approximately 85% of cases of lung cancer are due to cigarette smoking. This measure is an example of:*

a. An incidence rate
b. An attributable risk
c. A relative risk
d. A prevalence risk
e. A proportionate mortality ratio

Questions 2 and 3 refer to the following information:

The results of a 10-year cohort study of smoking and coronary heart disease (CHD) are shown below:

	OUTCOME AFTER 10 YEARS	
At Beginning of Study	**CHD Developed**	**CHD Did Not Develop**
2,000 Healthy smokers	65	1,935
4,000 Healthy nonsmokers	20	3,980

2. *The incidence of CHD in smokers that can be attributed to smoking is:* _____

3. *The proportion of the total incidence of CHD in smokers that is attributable to smoking is:* _____

Questions 4 and 5 are based on the following information:

In a cohort study of smoking and lung cancer, the incidence of lung cancer among smokers was found to be 9/1,000 and the incidence among nonsmokers was 1/1,000. From another source we know that 45% of the total population were smokers.

4. *The incidence of lung cancer attributable to smoking in the total population is:* _____

5. The proportion of the risk in the total population that is attributable to smoking is: _____

APPENDIX TO CHAPTER 13: LEVIN'S FORMULA FOR THE ATTRIBUTABLE RISK FOR THE TOTAL POPULATION

Another way to calculate this proportion for the total population is to use Levin's formula[4]:

$$\frac{p(r-1)}{p(r-1)+1}$$

where p is the proportion of the population with the characteristic or exposure and r is the relative risk (or odds ratio).

Leviton[5] has shown that Levin's formula[4] and the following formula are algebraically identical:

$$\frac{\left(\begin{array}{c}\text{Incidence in}\\ \text{total population}\end{array}\right)-\left(\begin{array}{c}\text{Incidence in}\\ \text{unexposed group}\end{array}\right)}{\text{Incidence in total population}}$$

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14

From Association to Causation: Deriving Inferences From Epidemiologic Studies

Not everything that can be counted counts, and not everything that counts can be counted.

—William Bruce Cameron, 1963[1]

LEARNING OBJECTIVES

- To describe a frequent sequence of study designs used to address questions of etiology in human populations.
- To differentiate between real and spurious associations in observational studies.
- To define the concepts of "necessary" and "sufficient" in the context of causal relationships.
- To present guidelines for judging whether an association is causal based on the guidelines set forth by the US Surgeon General and to discuss the application of these guidelines to broader questions of causal inference.
- To describe how the guidelines for causation originally proposed by the US Surgeon General have been modified and used by the US Public Health Service and the US Preventive Services Task Force.

In previous chapters, we discussed a variety of designs of epidemiologic studies that are used to determine whether an association exists between an exposure and a disease outcome (Fig. 14.1A). We then addressed different types of risk measurement that are used to quantitatively express an excess in risk. If we determine that an exposure is associated with a disease, the next question is whether the observed association reflects a causal relationship (see Fig. 14.1B).

Although Figs. 14.1A and B refer to an environmental exposure, they could just as well have specified a genetic characteristic or some other risk characteristic or a specific combination of environmental and genetic factors. As we shall see in the chapter on genetics and environmental factors, studies of disease etiology generally address the contributions of both genetic and environmental factors and their interactions.

This chapter discusses the derivation of causal inferences in epidemiology. Let us begin by asking, "What approaches are available for studying the etiology of disease?"

APPROACHES FOR STUDYING DISEASE ETIOLOGY

If we are interested in whether a certain substance is carcinogenic in human beings, a first step in the study of the substance's effect might be to expose animals to the carcinogen in a controlled laboratory environment. Although such animal studies afford us the opportunity to control the exposure dose and other environmental conditions and genetic factors precisely and to keep loss to follow-up to a minimum, at the conclusion of the study we are left with the problem of having to extrapolate data across species (i.e., from animal to human populations). Certain diseases seen in humans have neither occurred nor been produced, or reproduced, in animals. It is also difficult to extrapolate animal doses to

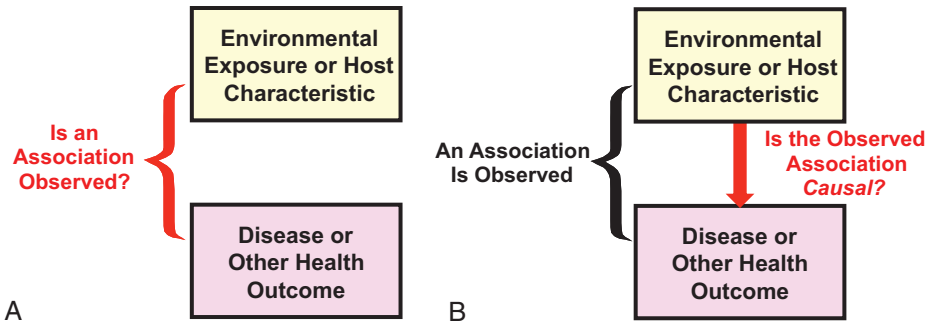

Fig. 14.1 **(A)** Do we observe an association between exposure and disease? **(B)** Is the observed association between exposure and disease causal?

human doses, and species differ in their responses. Thus, although such toxicologic studies can be useful, they still leave a gnawing uncertainty as to whether the animal findings can be generalized to human beings.

We can also use *in vitro* systems, such as cell culture or organ culture to establish causality. Although it is not uncommon for many biological or pathophysiological mechanisms, pathways are first initiated and observed in *in vitro* or pre-clinical animal studies, but these are artificial systems, and we are again left with the difficulty of extrapolating from artificial systems to intact, whole human organisms.

In view of these limitations, if we want to be able to draw a conclusion as to whether a substance *causes* disease in human beings, we need to make *observations in human populations*. Because we cannot ethically or practically randomize human beings to exposure to a suspected carcinogen (e.g., purposively expose human subjects to radon to "cause" cancer), we are dependent on nonrandomized observations, such as those that come from case-control and cohort studies.

Approaches to Etiology in Human Populations

Epidemiology often capitalizes on what have been called "unplanned" or "natural" experiments. (Some think that this phrase is a contradiction in terms, in that the word "experiment" implies a planned exposure or intervention.) What we mean by *unplanned* or *natural* experiments is that we take advantage of groups of people who have been exposed for non-study purposes, such as occupational cohorts in specific industries or persons exposed to toxic chemicals. Examples include people affected by the poison gas leak disaster at a pesticide manufacturing plant in Bhopal, India, in 1984 and residents of Hiroshima and Nagasaki, Japan, who were exposed to radiation from the atomic bombs dropped on both cities by US forces in 1945. Each of these exposed groups can be compared with an unexposed group (e.g., residents of Chennai, India or Tokyo, Japan) to determine whether there is an increased risk of a certain adverse effect in persons who have been exposed.

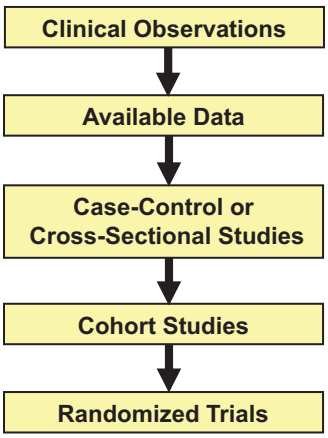

Fig. 14.2 A frequent sequence of studies in human populations.

In conducting human studies, the sequence shown in Fig. 14.2 is frequently followed. The initial step may consist of *clinical observations* at the bedside. For example, when the surgeon Alton Ochsner observed that virtually every patient on whom he operated for lung cancer gave a history of cigarette smoking, he was among the first to suggest a possible causal relationship.[2] A second step is to try to identify *routinely available data*, the analysis of which might shed light

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on the question. We can then carry out *new studies* such as the cohort and case-control studies, as discussed in prior chapters, which are specifically designed to determine whether there is an association between an exposure and a disease, and whether a causal relationship exists.

The usual first step in carrying out new studies to explore a relationship is often a *case-control study*. For example, if Ochsner had wanted to further explore his suggestion that cigarette smoking may be associated with lung cancer, he would have compared the smoking histories of a group of his patients with lung cancer with those of a group of patients without lung cancer—a case-control study. Given the specific design considerations of the case-control study, some investigators may opt to first explore the association in a cross-sectional study—Ochsner would ask a sample of general population about their smoking history and lung cancer. However, as we discussed earlier in Chapter 7, they can only be hypothesis-generating. Actually, it is not a good idea to infer causality from any single observational study, which is the reason why systematic reviews with or without meta-analyses are conducted.

If a case-control study yields evidence that a certain exposure is suspect, we might next do a *cohort study* (e.g., comparing smokers and nonsmokers and determining the risk of lung cancer in each group or comparing workers exposed to an industrial toxin with workers without such an exposure). Although, in theory, a randomized trial might be the next step, as discussed earlier, randomized trials are almost never used to study the effects of putative toxins or carcinogens and are generally used only for studying potentially *beneficial* agents.

Conceptually, a two-step process is followed in carrying out studies and evaluating evidence. However, in practice, this process often becomes interactive and deviates from a fixed sequence:

1. We determine whether there is an association or correlation between an exposure or characteristic and the risk of a disease. To do so, we use:
   a. Studies of group characteristics: ecologic studies (discussed in Chapter 7)
   b. Studies of individual characteristics: cohort, case-control, and other types of observational studies
2. If an association is demonstrated, we determine whether the observed association is likely to be a causal one.

TYPES OF ASSOCIATIONS

Real or Spurious Associations

Let us turn next to the types of associations that we might observe in a cohort or case-control study. If we observe an association, we start by asking the question, "Is it a true (real) association or a false (spurious/biased) one?" For example, if we designed a study to select controls in such a way that they tended to be unexposed, we might observe an association of exposure with disease (i.e., more frequent exposure in cases than in controls). This would not be a true association but only a result of the study design. Recall that this issue was raised in Chapter 7 regarding a study of coffee consumption and cancer of the pancreas. The possibility was suggested that the controls selected for the study had a lower risk of coffee consumption than was found in the general population.

Interpreting Real Associations

If the observed association is real, the next question is whether it is a causal association. Fig. 14.3 shows two possibilities. Fig. 14.3 A shows a causal association: we observe an association of exposure and disease, as indicated by the bracket, and the exposure induces development of the disease, as indicated by the arrow. Fig. 14.3 B shows the same observed association of exposure and disease, but they are associated only because they are both linked to a third factor, which is called a confounding variable (or *confounder*) and designated here as *factor X*. This association is a result of confounding and is noncausal. Confounding is discussed in greater detail in Chapter 15.

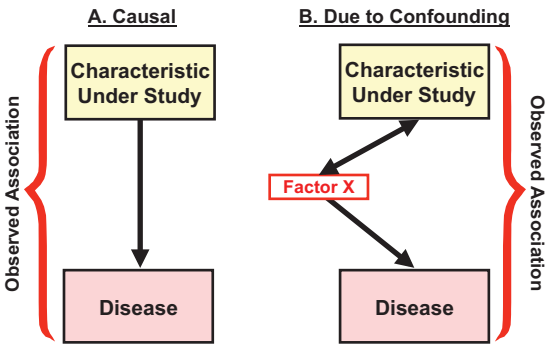

Fig. 14.3 Types of associations.

In Chapter 7 we discussed this issue in relation to McMahon's study of coffee and cancer of the pancreas. McMahon observed an association of coffee consumption with risk of pancreatic cancer. Cigarette smoking was known to be associated with pancreatic cancer, and coffee drinking and cigarette smoking are closely associated (few smokers at the time of that report did not drink coffee) (Fig. 14.4). Therefore, was the observed association of coffee drinking and cancer of the pancreas likely to be a causal relationship, or could the association be due to the fact that coffee and cigarette smoking are associated and that cigarette smoking is a known risk factor for cancer of the pancreas?

The same issue is exemplified by the observed association of physical inactivity and risk of colon cancer (Fig. 14.5). Is physical inactivity a causal factor for increased risk of colon cancer, or is the observed association due to confounding? That is, are we observing an association of physical inactivity and colon cancer because both are associated with a factor X (such as smoking), which might cause people to have both physical inactivity and an increased risk of colon cancer?

Is this distinction really important? What difference does it make? The answer is that it makes a tremendous difference from both clinical and public health standpoints. If the relationship is causal, we will succeed in reducing the risk of colon cancer if we promote physical activity, both for the individual but also at the population level. However, if the relationship is due to confounding, then the increased risk of colon cancer is caused by factor X. Therefore, increasing physical activity will have no effect on the risk of colon cancer. Thus, it is extremely important for us to be able to distinguish between an association due to a causal relationship and an association due to confounding (which is noncausal).

Let us look at another example. For many years it has been known that cigarette smoking by pregnant women is associated with low birth weight in their infants. As seen in Fig. 14.6 the effect is not just the result of the birth of a few low-birth-weight babies in this group of women. Rather, the entire weight distribution curve is shifted to the left in the babies born to smokers. The reduction in birth weight is also not a result of shorter pregnancies. The babies of smokers are smaller than those of nonsmokers at each gestational age (Fig. 14.7). A dose-response relationship is also seen (Fig. 14.8).

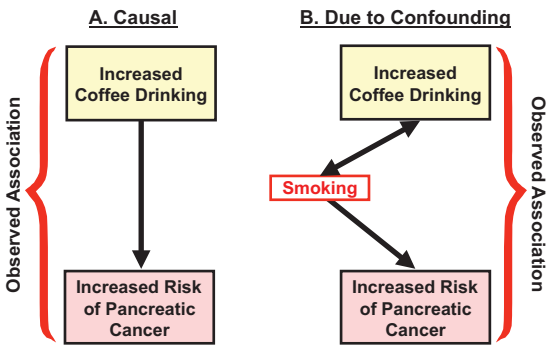

Fig. 14.4 Interpreting an observed association between increased coffee drinking and increased risk of pancreatic cancer.

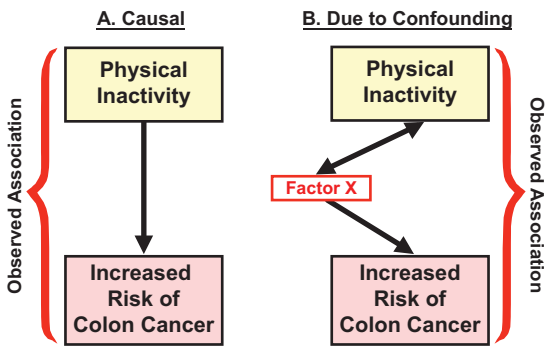

Fig. 14.5 Interpreting an observed association between increased physical inactivity and increased risk of colon cancer.

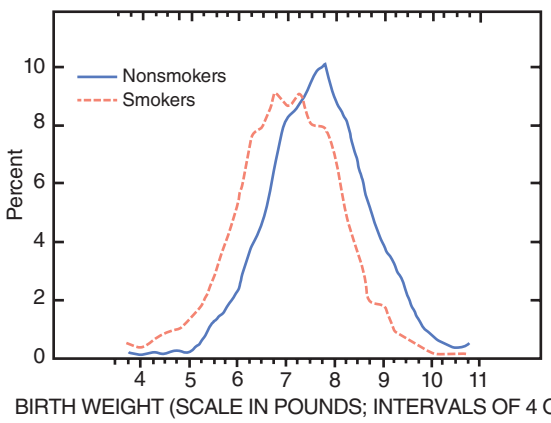

Fig. 14.6 Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those mothers who smoked 1 pack of cigarettes or more per day. (From US Department of Health, Education, and Welfare. *The Health Consequences of Smoking*. Washington, DC: Public Health Service; 1973:105.)

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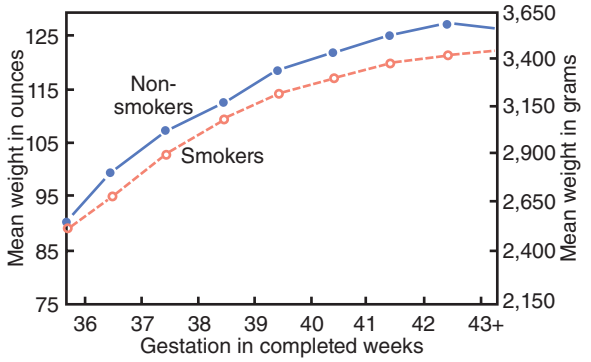

Fig. 14.7 Mean birth weight for week of gestation according to maternal smoking habit. (From US Department of Health, Education, and Welfare. *The Health Consequences of Smoking*. Washington, DC: Public Health Service; 1973:104.)

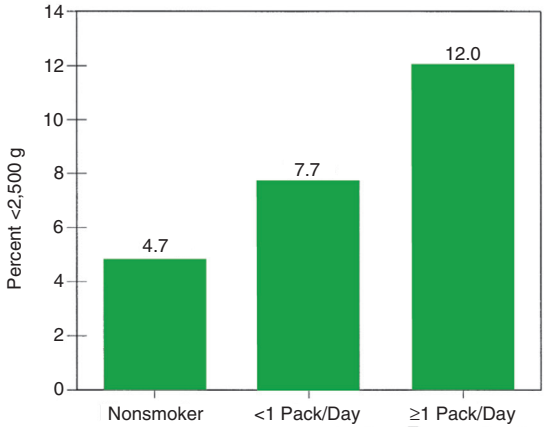

Fig. 14.8 Percentage of pregnancies (n = 50,267) with infant weighing less than 2,500 g, by maternal cigarette smoking category. (Redrawn from Ontario Department of Health. *Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals*. Vol. I. Toronto, Ontario: Department of Health, Ontario Perinatal Mortality Study Committee; 1967:275.)

The more a woman smokes, the greater her risk of having a low-birth-weight baby. For many years the interpretation of this association was the subject of great controversy. Many believed the association reflected a causal relation. Others, including a leading statistician, Jacob Yerushalmy, believed the association was due to confounding and was not causal. He wrote as follows:

> *A comparison of smokers and nonsmokers shows that the two differ markedly along many environmental, behavioral and biologic variables. For example, smokers are less likely to use contraceptives and to plan the pregnancy. Smokers are more likely to drink coffee, beer and whiskey and the nonsmoker, tea, milk and wine. The smoker is more likely than the nonsmoker to indulge in these habits to excess. In general, the nonsmokers are revealed to be more moderate than the smokers, who are shown to be more extreme and carefree in their mode of life. Some biologic differences are also noted between them: Thus, smokers have a higher twinning rate only in whites and their age for menarche is lower than for nonsmokers.*[3]

In view of these many differences between smokers and nonsmokers, Yerushalmy believed that it was not the *smoking* that caused the low birth weight but rather that the low weight was attributable to *other characteristics of the smokers*. It is interesting to examine a study that Yerushalmy carried out to support his position at the time (Fig. 14.9).[3]

Yerushalmy examined the results of one pregnancy (the study pregnancy) in a population of women who had had several pregnancies. The rate of low-birth-weight babies in the study pregnancy was 5.3% for women who were nonsmokers in *all* of their pregnancies. However, if they were smokers in all of their pregnancies, the rate of low birth weight in the study

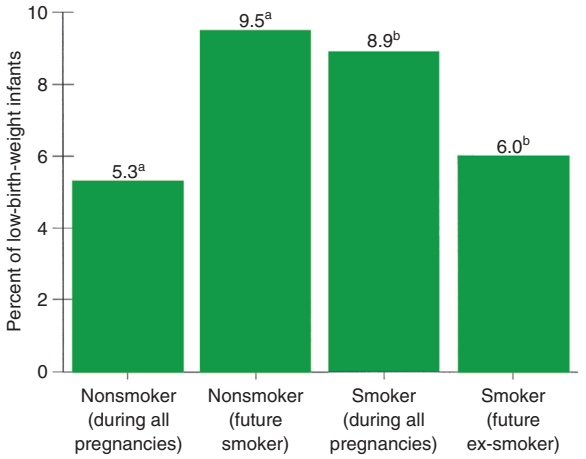

Fig. 14.9 Percentage of low-birth-weight infants by smoking status of their mothers ([a]$P < .01$; [b]$P < .02$). (Redrawn from Yerushalmy J. Infants with low birth weight born before their mothers started to smoke cigarettes. *Am J Obstet Gynecol*. 1972;112:277–284.)

pregnancy was almost 9%. When he examined pregnancies of women who were nonsmokers during the study pregnancy, but who later became smokers, he found that their rate of low-birth-weight babies was approximately equal to that of women who smoked in all pregnancies. When he examined pregnancies of women who were smokers in the study pregnancy but who subsequently stopped smoking, he found that their rate of low birth weight in the study pregnancy was similar to that of women who were nonsmokers in all of their pregnancies.

Based on these data, Yerushalmy came to the conclusion that it was not the smoking but rather some characteristic of the smoker that caused the low birth weight. Today, however, it is virtually universally accepted that smoking is a *cause* of low birth weight. The causal nature of this relation has also been demonstrated in randomized trials that have reduced the frequency of low birth weight by initiating programs for smoking cessation in pregnant women. (Note that we would not randomize pregnant women to smoke, but rather established causality by the randomization to the benefit of smoking cessation). Although this issue has now largely been resolved, it is illuminating to review both the controversy and the study because they exemplify the reasoning why it is necessary in trying to distinguish causal from noncausal interpretations of observed associations.

TYPES OF CAUSAL RELATIONSHIPS

A causal pathway can be either *direct* or *indirect* (Fig. 14.10). In *direct* causation a factor directly causes a disease without any intermediate step. In *indirect* causation a factor causes a disease but only through an intermediate step or steps. In human biology, intermediate steps are virtually always present in most causal processes.

If a relationship is causal, four types of causal relationships are possible: (1) necessary and sufficient; (2) necessary but not sufficient; (3) sufficient but not necessary; and (4) neither sufficient nor necessary.

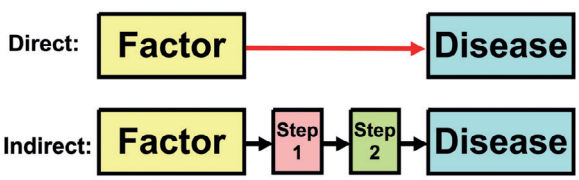

Fig. 14.10 Direct versus indirect causes of disease.

Necessary and Sufficient

In the first type of causal relationship, a factor is both necessary and sufficient for producing the disease. Without that factor, the disease never develops (the factor is necessary), and in the presence of that factor, the disease always develops (the factor is sufficient) (Fig. 14.11). This situation rarely if ever occurs. For example, in most infectious diseases, a number of people are exposed, some of whom will manifest the disease and others who will not. Members of households of a person with tuberculosis do not uniformly acquire the disease from the index case. In the recent SARS-CoV-2 pandemic we often observed families in which most members were identified to be infected, while one member never tested positive. If the exposure dose is assumed to be the same, there are likely differences in immune status, genetic susceptibility, or some other characteristics that determine who develops the disease and who does not. A one-to-one relationship of exposure to disease, which is a consequence of a necessary and sufficient relationship, rarely if ever occurs in humans.

Necessary but Not Sufficient

In another model, each factor is necessary but not in itself sufficient to cause the disease (Fig. 14.12). Thus, multiple factors are required, often in a specific

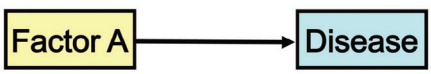

Fig. 14.11 Types of causal relationships: I. Factor A is both necessary and sufficient.

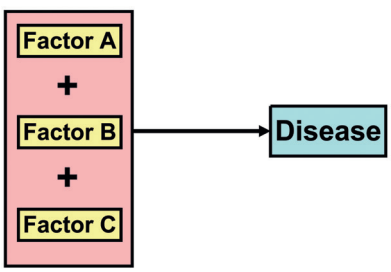

Fig. 14.12 Types of causal relationships: II. Each factor is necessary, but not sufficient.

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temporal sequence. For example, carcinogenesis is considered to be a multistage process involving both initiation and promotion. For a cancer to result, a promoter must act after an initiator has acted. Action of an initiator or a promoter alone will not produce a cancer.

Again, in tuberculosis, the tubercle bacillus is clearly a necessary factor, even though its presence may not be sufficient to produce the disease in every infected individual. Another example is the relationship of *Helicobacter pylori* to noncardiac gastric adenocarcinoma.[4] Although this bacterium is widely regarded as a necessary cause of this cancer, most individuals who are infected with *H. pylori* do not develop this cancer, a phenomenon that explains why *H. pylori* infection prevalence is very high in many populations, yet gastric adenocarcinoma remains relatively rare in these same populations. Thus, in addition to *H. pylori*, individuals must be exposed to other risk factors (e.g., smoking and intake of foods containing nitrates) to develop gastric cancer. (The relationship of *H. pylori* to gastric ulcers is discussed later in this chapter.)

Sufficient but Not Necessary

In this model the factor alone can produce the disease but so can other factors that are acting alone (Fig. 14.13). Thus, either radiation exposure or benzene exposure can each produce leukemia without the presence of the other. However, even in this situation, cancer does not develop in everyone who has experienced radiation or benzene exposure, so although both factors are not needed, other cofactors probably are. Thus, the criterion of *sufficient* is rarely met by a single factor.

Neither Sufficient nor Necessary

In the fourth model a factor by itself is neither sufficient nor necessary to produce disease (Fig. 14.14). This is a more complex model, which probably most accurately represents the causal relationships that operate in most chronic diseases. An example is that of the often nonoverlapping nature of risk factor clusters for the development of CHD; for instance, individuals may develop CHD if they are exposed to smoking, diabetes, and low high-density lipoprotein (HDL) or to a combination of hypercholesterolemia, hypertension, and physical inactivity. Each of these CHD risk factors is neither sufficient nor necessary. Interestingly, recognizing that many, if not most, individual risk factors are neither sufficient nor necessary, Rothman has proposed a model consistent with Fig. 14.14, in which a "sufficient cause" is formed by a *constellation* of risk factors, termed by him "component causes." In Rothman's conceptualization, a pie chart formed by a number of "component causes" represents the "sufficient cause." Thus Rothman's "sufficient cause" is actually a cluster of "component causes."[5] Hypothetical (yet not illogical) examples of Rothman-defined two "sufficient causes" for atherosclerotic disease are seen in Fig. 14.15.

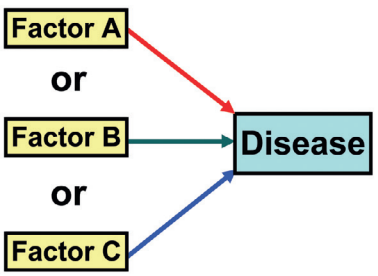

Fig. 14.13 Types of causal relationships: III. Each factor is sufficient, but not necessary.

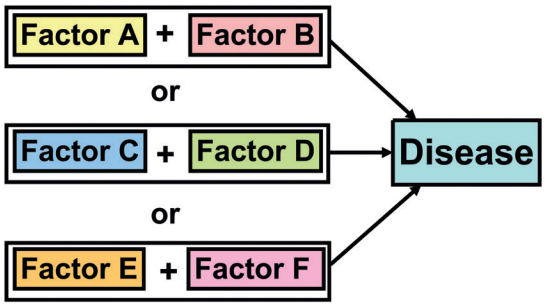

Fig. 14.14 Types of causal relationships: IV. Each factor is neither sufficient nor necessary.

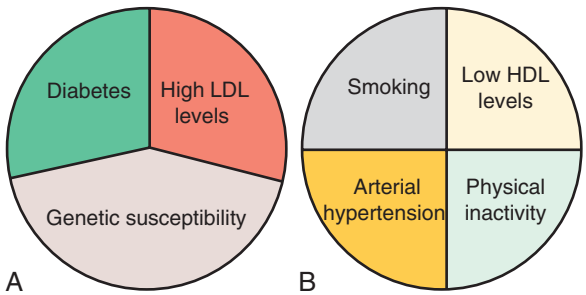

Fig. 14.15 (A–B) Hypothetical examples of sufficient causes of atherosclerotic disease. *HDL*, High-density lipoprotein; *LDL*, low-density lipoprotein.

EVIDENCE FOR A CAUSAL RELATIONSHIP

Many years ago, when the major disease problems faced by humans were primarily infectious in origin, the question arose as to what evidence would be necessary to prove that an organism causes a disease. In 1840, Henle proposed postulates for causation that were expanded by Koch in the 1880s.[6] The postulates for causation were as follows:

1. The organism is *always* found with the disease.
2. The organism is *not* found with any other disease.
3. The organism, when isolated from one who has the disease and cultured through several generations, produces the disease (in experimental animals).

Koch added that "[E]ven when an infectious disease cannot be transmitted to animals, the 'regular' and 'exclusive' presence of the organism [postulates 1 and 2] proves a causal relationship."[6]

These postulates, although not perfect, proved very useful for infectious diseases. However, as apparently noninfectious diseases assumed increasing importance toward the middle of the 20th century, the issue arose as to what would represent strong evidence of causation in diseases that were generally not of infectious origin. In such diseases there was no organism that could be isolated, cultured, and grown in animals. Specifically, as attention was directed to a possible relationship between smoking and lung cancer, the US Surgeon General appointed an expert committee to review the evidence. The committee developed a set of guidelines,[7] which have been revised many times over the years. The next few pages present a modified list of these guidelines (Box 14.1) with some brief comments.

BOX 14.1 Guidelines for Judging Whether an Observed Association Is Causal

1. Temporal relationship
2. Strength of the association
3. Dose-response relationship
4. Replication of the findings
5. Biologic plausibility
6. Consideration of alternate explanations
7. Cessation of exposure
8. Consistency with other knowledge
9. Specificity of the association

GUIDELINES FOR JUDGING WHETHER AN OBSERVED ASSOCIATION IS CAUSAL

In 1964, the Surgeon General's Advisory Committee on Smoking and Health published a report[8] describing a set of criteria to interpret evidence from epidemiologic studies for clinical and public health decision making. These were later presented by Sir Austin Bradford Hill in 1965.[9]

1. ***Temporal Relationship.*** It is clear that if a factor is believed to be the cause of a disease, exposure to the factor must occur before the disease develops. Fig. 14.16 shows the number of deaths per day and the mean concentration of airborne particles in London in early December 1952.[10] The pattern of a rise in particle concentration followed by a rise in mortality and a subsequent decline in particle concentration followed by a decline in mortality strongly supported the increase in mortality being due to the increase in air pollution. This example demonstrates the use of ecologic data for exploring a temporal relationship. Further investigation revealed that the increased mortality consisted almost entirely of respiratory and cardiovascular deaths and was highest in the elderly.

   It is often easier to establish a temporal relationship in a prospective cohort study than in a case-control study or a retrospective (nonconcurrent) cohort

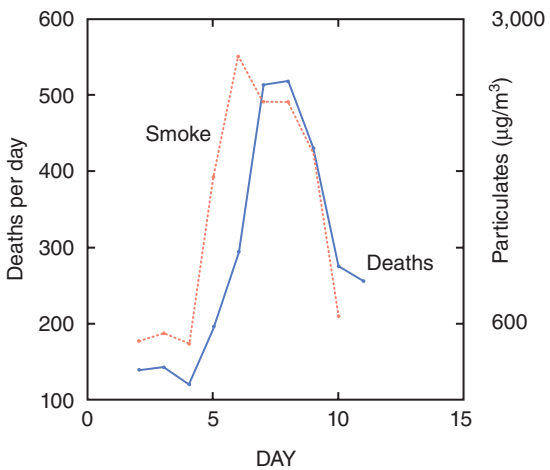

Fig. 14.16 The mean concentration of airborne particles (μg/m³) from the four inner monitoring stations in London and the count of daily deaths in the London Administrative County during the beginning of December 1952. (From Schwartz J. Air pollution and daily mortality: a review and meta analysis. *Environ Res.* 1994;64:36–52.)

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study. In the latter two types of studies, exposure information may need to be located (which may be difficult) or re-created from past records and the timing may therefore be imprecise.

The temporal relationship of exposure and disease is important not only for clarifying the *order* in which the two occur but also with regard to the *length of the interval* between exposure and disease. For example, asbestos has been clearly linked to increased risk of lung cancer, but the latent period between the exposure and the appearance of lung cancer is at least 15 to 20 years. Therefore, if, for example, lung cancer develops after only 3 years since the asbestos exposure, it is probably safe to conclude that the lung cancer was not a result of this exposure. It may also be difficult to establish the "exposure → disease" temporal sequence when a disease has a long subclinical ("silent") phase. For example, chronic lymphocytic leukemia may evolve subclinically for many years and, thus, when it is finally diagnosed, prior exposure to a factor may have occurred after the biological beginning of the disease.

2. ***Strength of the Association.*** The strength of the association is measured by the relative risk (or odds ratio). The stronger the association, the more likely it is that the relation is causal. For example, the relative risk for the relationship of high blood pressure (exposure) to stroke (outcome) is very high. In a population-based study conducted in Sweden, the relative risk was found to be greater than 5.4 in individuals with severe hypertension.[11] There is little or no doubt that high blood pressure levels cause stroke.
3. ***Dose-Response Relationship.*** As the dose of exposure increases, the risk of disease also increases. Fig. 14.17 shows an example of the dose-response relationship for cigarette smoking and lung cancer. Another example is given by the Swedish study mentioned above, in which, using normal blood pressure levels as the reference category, the adjusted relative risk for stroke increased in a graded fashion from 2.84 in individuals with prehypertension to 3.90 in those with moderately severe hypertension to 5.43 in those with levels consistent with severe hypertension. If a dose-response relationship is present, it is strong evidence for a causal relationship. However, the absence of a dose-response relationship does not necessarily rule out a causal relationship. In some cases in which a *threshold* may exist, no disease may develop up to a certain level of exposure (a threshold); above this level, disease may develop.

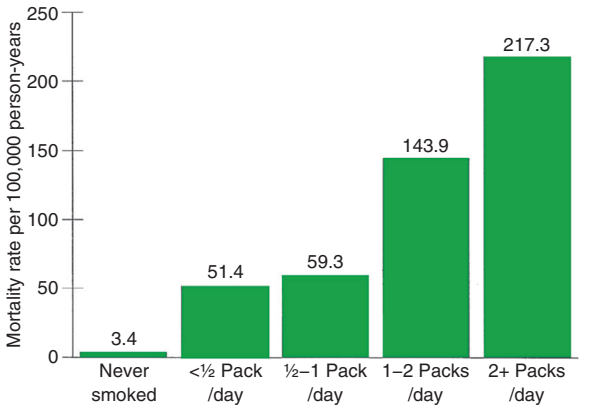

Fig. 14.17 Age-standardized death rates due to well-established cases of bronchogenic carcinoma (exclusive of adenocarcinoma) by current amount of smoking. (Modified from Hammond EC, Horn D. Smoking and death rates: report on 44 months of follow-up of 187,783 men: II. Death rates by cause. *JAMA*. 1958;166: 1294–1508. Copyright 1958, American Medical Association.)

4. ***Replication of the Findings.*** If the relationship is causal, we would expect to find it consistently in different studies and in different populations. Replication of findings is particularly important in epidemiology. If an association is observed, we would also expect it to be seen consistently within subgroups of the population and in different populations, unless there is a clear reason to expect different results.
5. ***Biologic Plausibility.*** Biologic plausibility refers to coherence with the current body of biologic knowledge. Examples may be cited to demonstrate that epidemiologic observations have sometimes preceded biologic knowledge. Thus, as discussed in an earlier chapter, Gregg's observations on rubella and congenital cataracts preceded any knowledge of teratogenic viruses. Similarly, the implication of high oxygen concentration in the causation of retrolental fibroplasia, a form of blindness that occurs in premature infants, preceded any biologic knowledge supporting such a relationship. Nevertheless, we seek consistency of the epidemiologic findings with existing biologic knowledge, and when this is not the case, interpreting the meaning of the observed association may be difficult. We may then be more demanding in

our requirements about the size and significance of any differences observed and in having the study replicated by other investigators in other populations.

6. ***Consideration of Alternate Explanations.*** We have discussed the problem in interpreting an observed association with regard to whether a relationship is causal or is the result of confounding. In judging whether a reported association is causal, the extent to which the investigators have taken other possible explanations into account and the extent to which they have ruled out such explanations are important considerations.
7. ***Cessation of Exposure.*** If a factor is a cause of a disease, we would expect the risk of the disease to decline when exposure to the factor is reduced or eliminated. Fig. 14.18 shows such historical data for cigarette smoking and lung cancer. Another example was the rapid decrease of CHD, diabetes, and stroke rates following a dramatic decrease in energy intake and thus obesity due to the Cuban economic crisis of 1989–2000.[12]

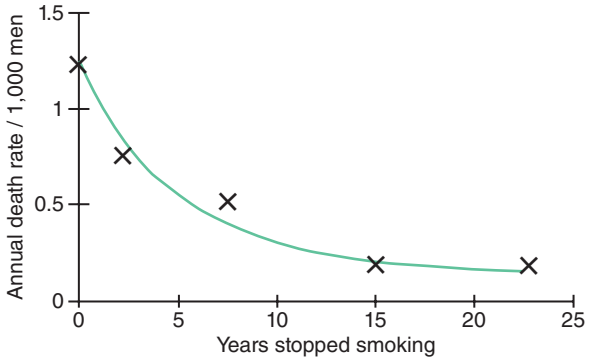

Fig. 14.18 Effects of terminating exposure: lung cancer death rates, standardized for age and amount smoked, among men continuing to smoke cigarettes and men who gave up smoking for different periods. The corresponding rate for nonsmokers was 0.07 per 1,000. (Modified from Doll R, Hill AB. Mortality in relation to smoking: ten years' observations of British doctors. *BMJ.* 1964;1:1399–1410.)

Eosinophilia-myalgia syndrome (EMS) reached epidemic proportions in 1989. Characterized by severe muscle pain and a high blood eosinophil count (white blood cells), the syndrome was found to be associated with manufactured preparations of L-tryptophan. In November 1989 a nationwide recall by the US Food and Drug Administration of over-the-counter preparations of L-tryptophan was followed by dramatic reductions in numbers of cases of EMS reported each month (Fig. 14.19). This is another example of a reduction in incidence being related to cessation of exposure, which

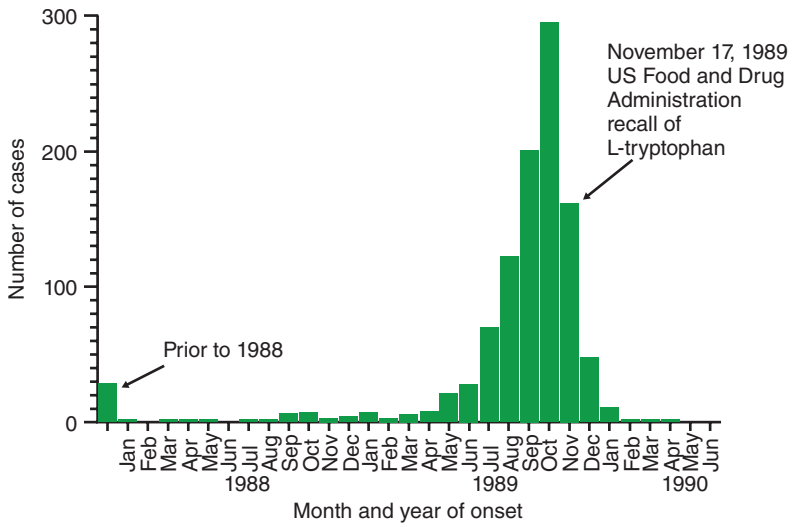

Fig. 14.19 Reported dates of illness onset by month and year for cases of eosinophilia-myalgia syndrome, as reported to the Centers for Disease Control and Prevention, Atlanta, as of July 10, 1990. (Modified from Swygert LA, Maes EF, Sewell LE, et al. Eosinophilia-myalgia syndrome: results of national surveillance. *JAMA.* 1990;264:1698–1703. Copyright 1990, American Medical Association.)

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adds to the strength of the causal inference regarding the exposure.

When cessation data are available, they provide helpful supporting evidence for a causal association. However, in certain cases the pathogenic process may have been irreversibly initiated and the disease occurrence may have been determined by the time the exposure is removed. Emphysema is not reversed with cessation of smoking, but its progression is reduced.

8. ***Consistency With Other Knowledge.*** If a relationship is causal, we would expect the findings to be consistent with other data. For example, Fig. 14.20 shows data regarding lung cancer rates in men and women and cigarette smoking in men and women.

   We see a consistent direction in the curves, with the increase in lung cancer rates following the increase in cigarette sales for both men and women. These data are consistent with what we would expect if the relationship between smoking and lung cancer is established as a causal one. Although the absence of such consistency would not completely rule out this hypothesis, if we observed rising lung cancer rates after a period of declining cigarette sales, for example, we would need to explain how this observation could be consistent with a causal hypothesis.

9. ***Specificity of the Association.*** An association is specific when a certain exposure is associated with only one disease; this is the weakest of all the guidelines and should probably be deleted from the list. Cigarette manufacturers have pointed out that the diseases attributed to cigarette smoking do not meet the requirements of this guideline because cigarette smoking has been linked to lung cancer, pancreatic cancer, bladder cancer, heart disease, emphysema, and other conditions.

   The possibility of such multiple effects from a single factor is not, in fact, surprising: regardless of the tissue that comprises them, all cells have common characteristics, including DNA, RNA, and various subcellular structures, so a single agent could have effects in multiple tissues. Furthermore, cigarettes are not a single factor but constitute a mixture of a large number of compounds; consequently, a large number of effects might be anticipated.

When specificity of an association is found, it provides additional support for a causal inference. However, as with a dose-response relationship, absence of specificity in no way negates a causal relationship.

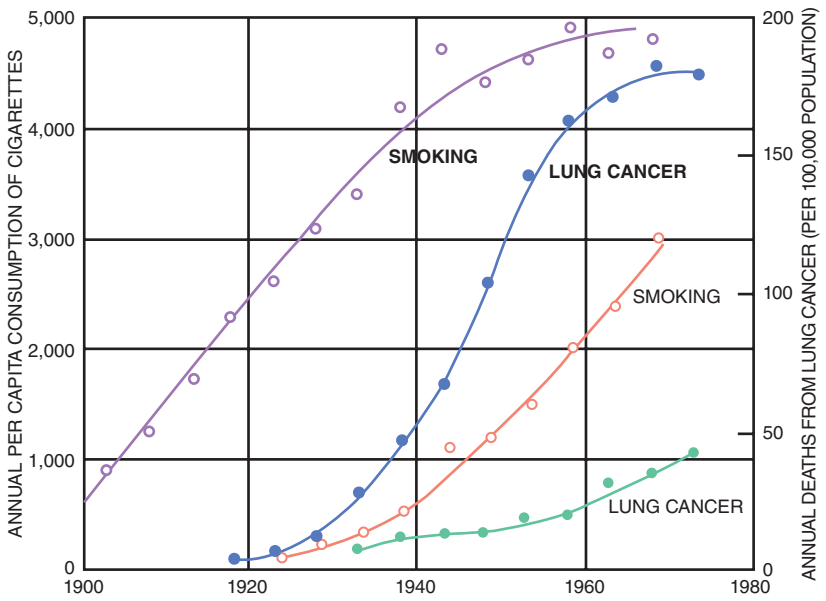

Fig. 14.20 Parallel trends between cigarette consumption and lung cancer in men *(two curves on left)* and in women *(two curves on right)* in England and Wales. (From Cairns J. The cancer problem. *Sci Am.* 1975;233:64–72, 77–78.)

Any conclusion that an observed association is causal is greatly strengthened when different types of evidence from multiple sources support such reasoning. Thus, it is not so much a count of the number of guidelines present that is relevant to causal inference but rather an *assessment of the total pattern of evidence observed* that may be consistent with one or more of the guidelines. Sir Austin Bradford Hill eloquently expressed this sentiment in an essay written in 1965:

> *Here then are nine different viewpoints [guidelines] from all of which we should study association before we cry causation. What I do not believe—and this has been suggested—that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?*[13]

DERIVING CAUSAL INFERENCES: TWO EXAMPLES

Peptic Ulcers and Gastric Cancer in Relation to Infection with *Helicobacter Pylori*

Although the preceding guidelines do not permit a quantitative estimation of whether an association is causal, they can nevertheless be very helpful, as seen in the following examples.

Until the 1980s the major causes of peptic ulcer disease were thought to be stress and lifestyle factors, including smoking. Peptic ulcer disease had long been attributed to the effects of gastric acid. Susceptibility to gastric acid had been linked to cigarette smoking, alcohol consumption, and use of nonsteroidal antiinflammatory agents. Therapy was primarily directed at inhibiting acid secretion and protecting mucosal surfaces from acid. Although these therapies helped healing, relapses were common.

In 1984 Australian physicians Drs. Barry J. Marshall and J. Robin Warren reported that they had observed small, curved bacteria colonizing the lower part of the stomach in patients with gastritis and peptic ulcers.[14] After several attempts, Marshall succeeded in cultivating a hitherto unknown bacterial species (later named *H. pylori*) from several of these biopsies (Fig. 14.21). Together they found that the organism was present in almost all patients with gastric inflammation or peptic ulcer. Many of these patients had biopsies performed which showed evidence of inflammation present in the gastric mucosa close to where the bacteria were seen. Based on these results, they proposed that *H. pylori* is involved in the etiology of these diseases. It was subsequently shown that the ulcer was often not cured until *H. pylori* had been eliminated.

It is now firmly established that *H. pylori* causes more than 90% of duodenal ulcers and up to 80% of gastric ulcers. The link between *H. pylori* infection and subsequent gastritis and peptic ulcer disease has been established through studies of human volunteers, antibiotic treatment studies, and epidemiologic studies. Thus, many of the study designs discussed in previous chapters and many of the guidelines for causal inferences discussed earlier in this chapter were involved in elucidating the role of *H. pylori* in peptic ulcer and gastritis. In 2005 the Nobel Prize for Physiology or Medicine was shared by Drs. Marshall and Warren "for their



Fig. 14.21 *Helicobacter pylori.* (Encyclopædia Britannica Online. http://www.britannica.com/EBchecked/topic/450889/peptic-ulcer?overlay=true&assemblyId=94921. Accessed November 2017.)

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discovery of the bacterium *H. pylori* and its role in gastritis and peptic ulcer disease."

Box 14.2 categorizes this evidence according to several of the guidelines for causation just discussed. Thus, as seen here, the guidelines can be extremely helpful in characterizing the evidence supporting a causal relationship.

Increasing evidence now also supports the association of *H. pylori* infection and the development of gastric cancer. Uemura and coworkers[15] prospectively studied 1,526 Japanese patients who had duodenal or gastric ulcers, gastric hyperplasia, or non-ulcer hyperplasia. Of this group, 1,246 had *H. pylori* infection and 280 did not. The mean follow-up period was 7.8 years. Gastric cancers developed in 36 (2.9%) of the infected patients but in none of the uninfected patients. Individuals who carry antibodies to *H. pylori* may have a two to three times higher risk of stomach cancer than those who do not (Fig. 14.22). The risk of stomach cancer also appears to be related to the type of strain of *H. pylori* which is infecting a person. Evidence is accumulating to support the idea that therapy against *H. pylori* may prevent gastric cancer. In the future, gastric cancer may come to be viewed as a largely preventable cancer of infectious origin.

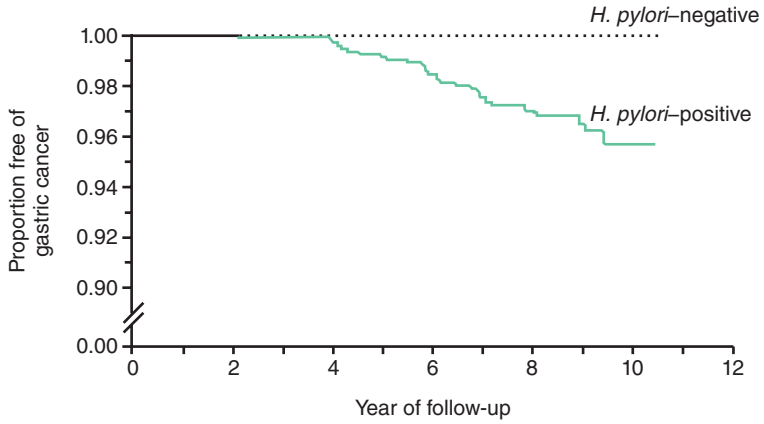
Age of Onset of Alcohol Use and Lifetime Alcohol Use Disorder

In 1997 Grant and Dawson[16] reported data on the relationship of age at first use of alcohol and prevalence of lifetime alcohol dependence and Alcohol Use Disorder. They analyzed data from 27,616 current and former

BOX 14.2 Assessment of the Evidence Suggesting Helicobacter Pylori as a Causative Agent of Duodenal Ulcers

1. Temporal relationship
   - *Helicobacter pylori* is clearly linked to chronic gastritis. Approximately 11% of chronic gastritis patients will go on to have duodenal ulcers over a 10-year period.
   - In one study of 454 patients who underwent endoscopy 10 years earlier, 34 of 321 patients who had been positive for *H. pylori* (11%) had duodenal ulcer compared with 1 of 133 *H. pylori*–negative patients (0.8%).
2. Strength of the association
   - *H. pylori* is found in at least 90% of patients with duodenal ulcer. In at least one population reported to lack duodenal ulcers, a northern Australian aboriginal tribe that is isolated from other people, it has never been found.
3. Dose-response relationship
   - Density of *H. pylori* per square millimeter of gastric mucosa is higher in patients with duodenal ulcer than in patients without duodenal ulcer. Also see item 2 above.
4. Replication of the findings
   - Many of the observations regarding *H. pylori* have been replicated repeatedly.
5. Biologic plausibility
   - Although originally it was difficult to envision a bacterium that infects the stomach antrum causing ulcers in the duodenum, it is now recognized that *H. pylori* has binding sites on antral cells and can follow these cells into the duodenum.
   - *H. pylori* also induces mediators of inflammation.
   - *H. pylori*–infected mucosa is weakened and is susceptible to the damaging effects of acid.
6. Consideration of alternate explanations
   - Data suggest that smoking can increase the risk of duodenal ulcer in *H. pylori*–infected patients but is not a risk factor in patients in whom *H. pylori* has been eradicated.
7. Cessation of exposure
   - Eradication of *H. pylori* heals duodenal ulcers at the same rate as histamine receptor antagonists.
   - Long-term ulcer recurrence rates were zero after *H. pylori* was eradicated using triple-antimicrobial therapy, compared with a 60%–80% relapse rate often found in patients with duodenal ulcers treated with histamine receptor antagonists.
8. Consistency with other knowledge
   - Prevalence of *H. pylori* infection is the same in men as in women. The incidence of duodenal ulcer, which in earlier years was believed to be higher in men than in women, has been equal in recent years.
   - The prevalence of ulcer disease is believed to have peaked in the latter part of the 19th century, and the prevalence of *H. pylori* may have been much higher at that time because of poor living conditions. This reasoning is also based on current observations that the prevalence of *H. pylori* is much higher in developing countries.
9. Specificity of the association
   - Prevalence of *H. pylori* in patients with duodenal ulcers is 90%–100%. However, it is found in some patients with gastric ulcer and even in asymptomatic individuals.

(Data from Megraud F, Lamouliatte H. *Helicobacter pylori* and duodenal ulcer: evidence suggesting causation. *Dig Dis Sci.* 1992;37:769–772; and DeCross AJ, Marshall BJ. The role of *Helicobacter pylori* in acid-peptic disease. *Am J Med Sci.* 1993;306:381–392.)



No. at risk

H. pylori–negative	280	272	251	245	213	57
H. pylori–positive	1,246	1,219	1,086	907	782	258

Fig. 14.22 Kaplan-Meier analysis of the proportion of *Helicobacter pylori*–positive and *H. pylori*–negative patients who remained free of gastric cancer. During follow-up, gastric cancer developed in 36 of the 1,246 *H. pylori*–infected patients (2.9%) but in none of the 280 uninfected patients ($P < .001$). (From Uemura N, Okamoto S, Yamomoto S, et al. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 2001; 345:784–789.)

drinkers who were interviewed as part of the 1992 National Longitudinal Alcohol Epidemiologic Survey. The rates of lifetime *dependence* decreased from more than 40% among individuals who began drinking at age 14 years or younger to approximately 10% among those who started drinking at age 20 years or older (Fig. 14.23). The configuration of the curve in Fig. 14.23 suggests a dose-response relationship as has been observed for longer duration of smoking associated with increased risk of lung cancer. However, the data may also point to a period of particularly high susceptibility, namely, that the period of preadolescence and early adolescence is a period of increased risk for developing a disorder of alcohol use. Therefore, preventive interventions should be targeted to this group in the hope of delaying drinking onset. However, adopting such an approach assumes that the relationship between early onset of drinking and subsequent lifetime alcohol use disorder is a causal one, so that delaying age at onset of drinking would reduce the risk of lifetime alcohol dependence. Another possible explanation is that those who are destined for lifetime alcohol dependence tend to begin drinking earlier but that the earlier age at drinking onset is not necessarily a cause of the later dependence. Further research is therefore needed to explain the intriguing association that has been observed. We shall return to this example in Chapter 16.

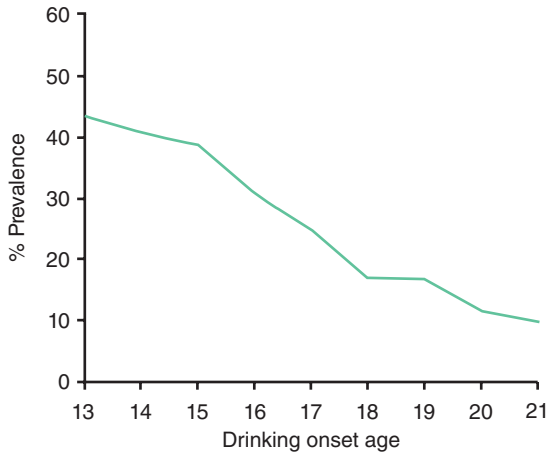


Fig. 14.23 Relation of age of onset of alcohol use to prevalence of lifetime alcohol use disorder. (Modified from Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse.* 1997;9: 103–110.)

MODIFICATIONS OF THE GUIDELINES FOR CAUSAL INFERENCES

In 1986 the US Public Health Service brought together a group of 19 experts to examine the scientific basis of the content of prenatal care and to answer the question:

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Which measures implemented during prenatal care have actually been demonstrated to be associated with improved outcome? The panel's report was issued in 1989 and served as the basis of a comprehensive report.[17] As the panel began its deliberations, it became clear that questions of causation were at the heart of the panel's task and that guidelines were needed for assessing the relationship of prenatal measures to health outcomes. A subcommittee reviewed the current guidelines (just enumerated in the preceding text) and defined a process for using evidence that includes (1) categorization of the evidence by the quality of its sources and (2) evaluation of the evidence of a causal relationship using standardized guidelines.[18] These recommendations are excerpted in Box 14.3. Although these modified guidelines clearly use the original components, they establish reasonable priorities in weighting them. They thus define an approach for looking at causation that may have

BOX 14.3 Process for Using the Evidence in Developing Recommendations on the Effectiveness of Prenatal Interventions

Stage I: Categorizing the Evidence by the Quality of Its Source. ***(In each category, studies are listed in descending order of quality.)***

1. Trials (planned interventions with contemporaneous assignment of treatment and nontreatment)
   a. Randomized, double-blind, placebo-controlled with sufficient power appropriately analyzed.
   b. Randomized but blindness not achieved.
   c. Nonrandomized trials with good control of confounding, that are well conducted in other respects.
   d. Randomized but with deficiencies in execution or analysis (insufficient power, major losses to follow-up, suspect randomization, analysis with exclusions).
   e. Nonrandomized trials with deficiencies in execution or analysis.
2. Cohort or case-control studies
   a. Hypothesis specified before analysis, good data, confounders accounted for.
   b. As above but hypothesis not specified before analysis.
   c. Post hoc, with problem(s) in the data or the analysis.
3. Time-series studies
   a. Analyses that take confounding into account.
   b. Analyses that do not consider confounding.
4. Case-series studies: Series of case reports without any specific comparison group

Among other issues that must be considered in reviewing the evidence are the precision of definition of the outcome being measured, the degree to which the study methodology has been described, adequacy of the sample size, and the degree to which characteristics of the population studied and of the intervention being evaluated have been described.

A study can be well designed and carried out in an exemplary fashion (internal validity), but if the population studied is an unusual or highly selected one, the results may not be generalizable (external validity).

Stage II: Guidelines for Evaluating the Evidence of a Causal Relationship. ***(In each category, studies are listed in descending priority order.)***

1. Major criteria
   a. Temporal relationship: An intervention can be considered evidence of a reduction in risk of disease or abnormality only if the intervention was applied before the time the disease or abnormality would have developed.
   b. Biologic plausibility: A biologically plausible mechanism should be able to explain why such a relationship would be expected to occur.
   c. Consistency: Single studies are rarely definitive. Study findings that are replicated in different populations and by different investigators carry more weight than those that are not. If the findings of studies are inconsistent, the inconsistency must be explained.
   d. Alternative explanations (confounding): The extent to which alternative explanations have been explored is an important criterion in judging causality.
2. Other considerations
   a. Dose-response relationship: If a factor is indeed the cause of a disease, usually (but not invariably) the greater the exposure to the factor, the greater the risk of the disease. Such a dose-response relationship may not always be seen because many important biologic relationships are dichotomous and reach a threshold level for observed effects.
   b. Strength of the association: The strength of the association is usually measured by the extent to which the relative risk or odds depart from unity, either greater than 1 (in the case of disease-causing exposures) or less than 1 (in the case of preventive interventions).
   c. Cessation effects: If an intervention has a beneficial effect, the benefit should cease when it is removed from a population (unless carryover effect is operant).

(Modified from Gordis L, Kleinman JC, Klerman LV, et al. Criteria for evaluating evidence regarding the effectiveness of prenatal interventions. In: Merkatz IR, Thompson JE, eds. *New Perspectives on Prenatal Care*. New York: Elsevier; 1990:31–38.)

applicability far beyond questions of the effectiveness of prenatal measures.

A similar approach, ranking studies by the quality of the study and its evidence, is used by the US Preventive Services Task Force, which is responsible for developing clinical practice guidelines for prevention and screening (Table 14.1).[19] The Task Force is an independent committee of experts supported by the US government. Members include experts in primary care, prevention, evidence-based medicine, and research methods. Various clinical areas and experience in preventive medicine, public health, and health policy are also represented.

For each topic the Task Force considers, it defines the questions that need to be addressed and identifies and retrieves the relevant evidence. The quality of each individual study is assessed, after which the strength of the totality of available evidence is judged. Estimates are made of the balance of benefits and harms. This balance is expressed as the net benefit (the difference between benefits and harms). The Task Force prepares recommendations for preventive interventions based on these considerations.

Fig. 14.24 shows a generic example of the analytic plan prepared by the Task Force as a framework for evaluating the evidence for a screening program. The straight arrows show possible pathways of benefit, and the curved arrows show possible adverse effects relating to different stages. The primary question (question 1 in the figure) is generally one of whether screening is effective in reducing the risk of an adverse outcome such as mortality and, if so, to what extent.

Deliberations of the Task Force often deal with the different steps or linkages that comprise this overall pathway. The arrow in the figure (step 5) shows the relation of treatment to outcome. Other arrows in the figure, steps 3, 4, and 6, show individual components of question 1. These assessments generally depend on a review of relevant randomized trials to prepare a chain of supporting evidence on which to base an answer to question 1. The evidence for each linkage is summarized in the evidence review and then summarized across the different linkages to provide an overall assessment of the supporting evidence for the preventive service being evaluated.

TABLE 14.1 US Preventive Services Task Force Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from a multitude of well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on the desired health outcomes. Because of the precision of findings, this conclusion is therefore unlikely to be strongly affected by the results of future studies. These recommendations are often based on direct evidence from clinical trials of screening or behavioral interventions. High-quality trials designed as "pragmatic" or "effectiveness" trials are often of greater value in understanding external validity
Moderate	The available evidence is sufficient to determine the effects of the preventive service on targeted health outcomes, but confidence in the estimate is constrained by factors such as: • The number, size, or quality of individual studies in the evidence pool • Some heterogeneity of outcome findings or intervention models across the body of studies • Mild to moderate limitations in the generalizability of findings to routine primary care practice. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The very limited number or size of studies • Inconsistency of direction or magnitude of findings across the body of evidence • Critical gaps in the chain of evidence • Findings are not generalizable to routine primary care practice • A lack of information on prespecified health outcomes • Lack of coherence across the linkages in the chain of evidence More information may allow an estimation of effects on health outcomes.

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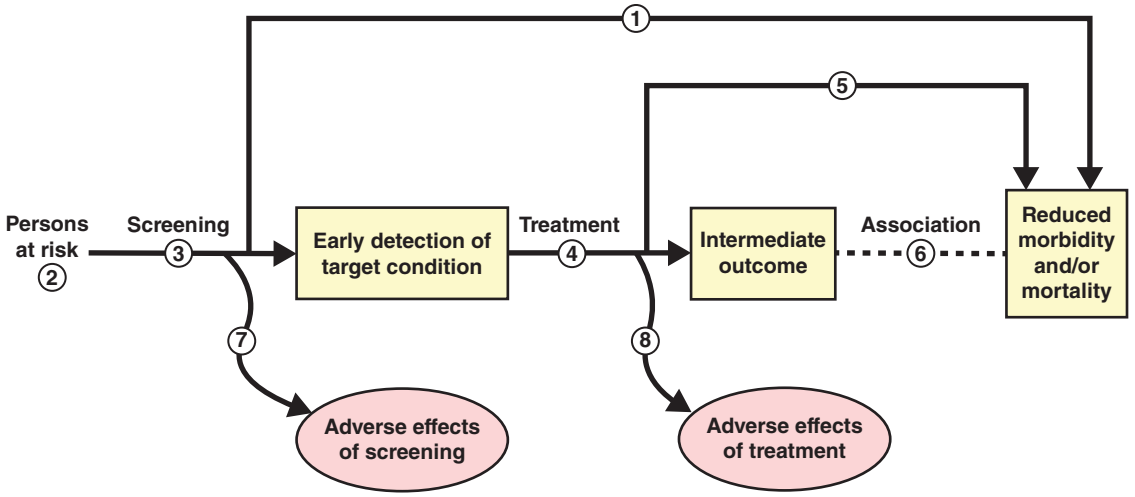

Fig. 14.24 Template of an analytic framework. (From US Preventive Services Task Force. USPSTF Procedure Manual. May 2021. https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/inline-files/procedure-manual-2022.pdf)

The certainty of net benefit is graded on a three-point scale: high, moderate, or low (see Table 14.1). The recommendations of the Task Force are based on a combined consideration of the certainty and the magnitude of the net benefit, as shown in the matrix in Table 14.2, in which a grading system of A, B, C, D, and *Insufficient* is used. The meaning of each grade is explained in Table 14.3.

The work of the Task Force has dealt with screening for many diseases and conditions. Some examples will illustrate the breadth of the Task Force's activities. It has reviewed the evidence for screening for different cancers, for cardiovascular diseases, including hypertension, CHD, and abdominal aortic aneurysm, for infectious diseases, including gonorrhea, syphilis, chlamydia, and hepatitis B and C, and for mental conditions such as dementia, depression, and suicide risk, and screening for glaucoma and for type 2 diabetes. The Task Force has also reviewed the evidence for the effectiveness of counseling for many conditions such as counseling to prevent tobacco use and tobacco-related diseases, counseling to prevent alcohol misuse, counseling to promote a healthy diet, and counseling to promote physical activity, among others. The aforementioned issues have been addressed in adults, but childhood conditions have also been reviewed by the Task Force, including prevention of dental caries in preschool children, screening for scoliosis in adolescents, newborn hearing screening, screening for visual impairment in children younger than 5 years of age, and screening for obesity in children and adolescents. These and many more evidence reviews and recommendations of the Task Force can be found on the website of the Agency for Health Care Research and Quality (https://www.ahrq.gov). The deliberations and recommendations of the Task Force provide a

TABLE 14.2 US Preventive Services Task Force Recommendation Grade Grid: Certainty of Net Benefit and Magnitude of Net Benefit

	MAGNITUDE OF NET BENEFIT			
Certainty of Net Benefit	**Substantial**	**Moderate**	**Small**	**Zero/Negative**
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient			

TABLE 14.3 How to Interpret Task Force Recommendation Grades

Grade	Definition	Suggestions for Practice
A	The US Preventive Services Task Force (USPSTF) recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

highly useful model of assessing the strength of the evidence and moving from causal inferences to policy recommendations.

CONCLUSION

Although causal guidelines discussed in this chapter are often referred to as *criteria*, this term does not seem entirely appropriate. These should not also be used as a checklist. However, a holistic approach to evaluating the causal association between a certain exposure and a certain outcome should be exercised in light of these guidelines. While it may be a desirable goal to place causal inferences on a firm quantitative and structural foundation, at present, we generally do not have all the information needed for doing so. The list presented in this chapter should therefore only be considered as guidelines that can be of most value when coupled with reasoned judgment about the entire body of available evidence in making decisions about causation.

In the next chapter, we address several additional issues that need to be considered in deriving causal inferences from epidemiologic studies.

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REVIEW QUESTIONS FOR CHAPTER 14

1. *In a large case-control study of patients with pancreatic cancer, 17% of the patients were found to be diabetic at the time of diagnosis, compared with 4% of a well-matched control group (matched by age, sex, ethnic group, and several other characteristics) that was examined for diabetes at the same time as the cases were diagnosed. It was concluded that the diabetes played a causal role in the pancreatic cancer. This conclusion:*

a. Is correct
b. May be incorrect because there is no control or comparison group
c. May be incorrect because of failure to establish the time sequence between onset of the diabetes and diagnosis of pancreatic cancer
d. May be incorrect because of less complete ascertainment of diabetes in the pancreatic cancer cases
e. May be incorrect because of more complete ascertainment of pancreatic cancer in nondiabetic persons

2. *An investigator examined cases of fetal death in 27,000 pregnancies and classified mothers according to whether they had experienced sexual intercourse within 1 month before delivery. It was found that 11% of the mothers of fetuses that died and 2.5% of the mothers of fetuses that survived had had sexual intercourse during the period. It was concluded that intercourse during the month preceding delivery caused the fetal deaths. This conclusion:*

a. May be incorrect because mothers who had intercourse during the month before childbirth may differ in other important characteristics from those who did not
b. May be incorrect because there is no comparison group
c. May be incorrect because prevalence rates are used where incidence rates are needed
d. May be incorrect because of failure to achieve a high level of statistical significance
e. Both *b* and *c*

3. *All of the following are important criteria when making causal inferences except:*

a. Consistency with existing knowledge
b. Dose-response relationship
c. Consistency of association in several studies
d. Strength of association
e. Predictive value

Questions 4 and 5 are based on the following information:

Factor A, B, or C can each individually cause a certain disease without the other two factors but only when followed by exposure to factor X. Exposure to factor X

alone is not followed by the disease, but the disease never occurs in the absence of exposure to factor X.

4. *Factor X is:*
   - **a.** A necessary and sufficient cause
   - **b.** A necessary but not sufficient cause
   - **c.** A sufficient but not necessary cause
   - **d.** Neither necessary nor sufficient
   - **e.** None of the above

5. *Factor A is:*
   - **a.** A necessary and sufficient cause
   - **b.** A necessary but not sufficient cause
   - **c.** A sufficient but not necessary cause
   - **d.** Neither necessary nor sufficient
   - **e.** None of the above

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15

More on Causal Inference: Bias, Confounding, and Interaction

LEARNING OBJECTIVES

- To review some possible biases in epidemiologic studies, including selection bias and information bias.
- To define confounding and to discuss possible ways to deal with confounding in the design and/or analysis of an observational (nonrandomized) study.
- To define interaction and to present a framework for detecting whether (and to what extent) two factors interact to influence the risk of a disease.

In this chapter, we expand on the discussion of causation that was begun in Chapter 14. We now focus on three important issues in making causal inferences: (1) bias, (2) confounding, and (3) interaction. These three issues are important for any type of study design, although if a randomized study is done properly, bias and confounding will be kept to a minimum. Examples of each issue are described in the context of specific study designs, but it should be kept in mind that these issues can affect all types of study designs and are not limited to the types of studies that have been selected as examples in this chapter.

BIAS

Bias has been addressed in many of the previous chapters because it is a major consideration in any type of epidemiologic study design and is considered a threat to the internal validity (and, thus, also to the external) of the epidemiologic study design. Therefore only a few additional comments will be made here.

What do we mean by *bias?* Bias has been defined as "any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease."[1]

Selection Bias

What types of bias do we encounter in epidemiologic studies? The first is *selection bias.* If the way in which cases and controls, or exposed and unexposed individuals, were selected is such that an apparent association is observed—even if, in reality, exposure and disease are not associated—the apparent association is the result of selection bias. In other words, selection bias arises from including individuals in the study, or in the analytic dataset, who are not supposed to be included ("immigrative selection bias"), and excluding individuals in the study who are not supposed to be excluded from the study, or the analytic dataset ("emigrative selection bias").

Selection bias may also result from nonresponse of potential study participants. For example, if we are studying the possible relationship of an exposure and a disease outcome and the response rate of potential subjects is higher in people with the disease who were exposed than in people with the disease who were not exposed, an apparent association could be observed even if, in reality, there is no association. Alternatively, the association, even if real, may be inflated by having greater participation among people with the disease who were exposed. The opposite may also lead to bias (i.e., when those who are both diseased and exposed are less likely to participate in the study).

In general, people who refuse to participate in a study often differ from those who participate in regard to many demographic, socioeconomic, cultural, lifestyle, and health status factors.[2] One study that attempted to

characterize nonresponders was reported by Ronmark et al. in 1999.[3] In the course of carrying out a prevalence study of asthma, chronic bronchitis, and respiratory symptoms, they studied the characteristics of nonresponders and the reasons for nonresponse. In this study, 9,132 people living in Sweden were invited to participate. Data were obtained by a mailed questionnaire, and the response rate was 85%. A sample of nonresponders was contacted by telephone and interviewed using the same questionnaire used in the main study. The authors found a significantly higher proportion of current smokers and manual laborers among the nonresponders than among the study participants. In addition, the prevalence rates of wheezing, chronic cough, sputum production, attacks of breathlessness, asthma, and use of asthma medications were significantly higher among the nonresponders than among the responders. Thus, the study inferences were diminished by the loss of participation from the nonresponders, and the associations that were found in the respondents were thus skewed toward the null.

In most studies no information can be obtained from the nonresponders, and hence nonresponse may introduce a serious bias into the study that may be difficult (or perhaps impossible) to assess. It is therefore important to keep nonresponse in epidemiologic studies to a minimum. For example, the UK Biobank recruited 500,000 men and women ages 40 to 69 over 5 years to evaluate risk factors for the major diseases of middle and old age.[4] While a very large number for a cohort study, only 5% of the adults approached agreed to participate in the study. The extent to which the recruited sample represents the target population may be of concern. However, since all UK citizens are included in the National Health Service, comparisons of the cohort to the target population can be estimated. In addition, any nonresponders should be characterized as much as possible by using whatever information is available to determine ways in which they differ from responders (estimated age, sex, geographic location, etc.) and to gauge the likely impact of their nonresponse on the results of the study.

In cohort studies, participant losses during follow-up may also result in selection bias, which is the most common mechanism of *emigrative* selection bias. However, since there is baseline information on these losses at the time of enrollment, it is possible to compare those who are lost with those who are not lost to observation on a number of sociodemographic and other factors. In the United States and other countries, it is also possible to link information on nonrespondents to a national death registry, thus allowing a comparison of mortality rates of the outcome under study for respondents and nonrespondents. This type of linkage is particularly useful when the primary outcome of the study is mortality.[5–8] It is important to keep in mind the distinction between *selecting subjects for a study* and *selection bias.* Virtually every study conducted in human populations selects study subjects from a larger (target) population. The nature of this selection potentially affects the *generalizability* or *external validity* of the study but does not necessarily affect the validity of the comparisons made within the study or the study's *internal validity.* On the other hand, when a systematic error is made in selecting one or more of the study groups that will be compared, *selection bias* may result. Such a bias can result in odds ratios (ORs) or relative risks (RRs) that may not be correct estimates and consequently lead to invalid inferences regarding the associations of exposure and disease. Selection bias can therefore arise as an error in selecting a study group or groups within the study and can have a major impact on the internal validity of the study and the legitimacy of the inference regarding the association of exposure and outcome. Selecting the study population from a larger target population should not be confused with selection bias, which results from a systematic error in selecting subjects in one or more of the study groups, such as exposed or unexposed participants, or cases or controls.

An interesting "classic" example of selection bias was demonstrated in 1974 with the publication of data that appeared to suggest a relationship between use of reserpine (a commonly used antihypertensive agent) and the risk of breast cancer. Three articles supporting such an association were published in the same issue of the *Lancet* in September 1974.[9–11] The three papers reported three studies conducted in Boston, Great Britain, and Helsinki, respectively.

Let's consider one of these articles, which exemplifies the problem of selection bias. Heinonen et al.[11] reported a matched-pair case-control study carried out in surgical patients at a hospital in Helsinki. Women with breast cancer were compared with women without breast cancer in terms of use of reserpine. Women with newly diagnosed breast cancer were identified from a hospital discharge register and from records that logged operations at the hospital. They served as "cases," and each

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TABLE 15.1 Results of a Matched-Pairs Analysis of a Case-Control Study of Reserpine Use and Breast Cancer

Breast Cancer Cases	Controls: *Used Reserpine*	Controls: *Did Not Use Reserpine*
Used Reserpine	8	45
Did Not Use Reserpine	23	362

$$\text{Matched-pairs odds ratio} = \frac{45}{23} = 1.96$$

Modified from Heinonen OP, Shapiro S, Tuominen L, Turunen MI. Reserpine use in relation to breast cancer. *Lancet.* 1974; 2:675–677.

was pair-matched by age and year of her operation to a control who was a woman admitted for elective surgery for some benign condition. A total of 438 case-control pairs were available for analysis. As seen in Table 15.1, there were 45 pairs in which the case used reserpine and the control did not, and 23 pairs in which the control used reserpine and the case did not. The resulting matched pair odds ratio (OR) was 45/23, or 1.96.

A problem was recognized, however, in the method used for selecting controls. In selecting the controls, the authors excluded women who had had the following surgeries: cholecystectomy, thyroidectomy for thyrotoxicosis, surgery for renal disease, and any cardiac operation, sympathectomy, or vascular graft. They were excluded because at the time the study was conducted, reserpine was one of the agents often used in treating these conditions. The authors were concerned that if patients with these conditions were included in this case-control study, the prevalence of reserpine use in the controls would be artificially high, so that even if reserpine use was increased in breast cancer cases, the increase might not be detected.

Unfortunately, in trying to address this concern, the authors created a different problem because these exclusions were not applied to the cases. By excluding patients with these conditions from the controls, they created a control group in which the prevalence of reserpine use was artificially lower because a large group of potential reserpine users was excluded. Thus, even if reserpine use was not increased in women who developed breast cancer, this study could show a difference in reserpine use between the cases and the controls only because of the way the controls were selected.

This type of selection bias has been called *exclusion bias.*[12] It results when investigators apply different eligibility ("inclusion") criteria to the cases and to the controls, with regard to which clinical conditions in the past would permit eligibility in the study and which would serve as the basis for exclusion. Horwitz and Feinstein[12] tried to replicate the reserpine study in 257 women with breast cancer and 257 controls, calculating ORs in two ways: first, including all the women and, second, after excluding from the controls women with a history of cardiovascular disease. The OR including all women was 1.1, but when women with cardiovascular disease were excluded, the OR rose to 2.5. These findings support the suggestion that the apparent relation of reserpine use and breast cancer in the Helsinki study resulted from selection bias due to the different criteria for selecting controls in the study. The study that dealt with coffee drinking and pancreatic cancer[13] had a similar problem, as discussed in Chapter 7.

The application of the same eligibility criteria to the selection of cases and controls should ideally result in the phenomenon coined by Schlesselman as *compensating bias.*[1] A corollary of this notion is that when the bias in selecting cases and controls is of the same magnitude, compensating bias is achieved. A hypothetical example of compensating bias is a case-control study in which both cases and controls are identified through a screening program. Individuals who decide to undergo a screening examination do not know before the screening whether they will be cases or controls, and thus the self-selection for screening is independent of the screening result. In colon cancer, for example, individuals who choose to undergo a colonoscopy are more likely to have a family history of colon cancer and to have a history of colon polyps. However, as the self-selection process is the same for those who are subsequently found to have colon cancer and those who are not, compensating bias is achieved and, as a result, the OR is unbiased. In other words, these selection factors (family history and a history of colon polyps) are equally inflated (biased) in

both cases and controls, and thus when calculating the OR, the "inflation (bias) factor" cancels out. If individuals with a family history of colon cancer are twice as likely to be included in the study, then:

$$\text{Odds Ratio} = \frac{\text{Odds of exposure in cases} \times 2.0}{\text{Odds of exposure in controls} \times 2.0}$$
$$= \frac{\text{Odds of exposure in cases}}{\text{Odds of exposure in controls}} \times 1.0$$
$$= \text{True Odds Ratio}$$

This example explains why the measure of association may be unbiased even if each exposure frequency is biased, thus highlighting the difference between validity of an absolute measure of frequency (biased odds) and validity of a measure of association (unbiased odds ratio).

Information Bias

Information bias can occur when the means for obtaining information about the subjects in the study are flawed so that some of the information gathered regarding exposures and/or disease outcomes is incorrect. This is also called *misclassification bias*.

Given inaccuracies in methods of data acquisition, we may at times misclassify subjects and thereby introduce a misclassification bias. For example, in a case-control study, some people who have the disease (cases) may be unknowingly misclassified as controls, and some without the disease (controls) may be misclassified as cases. This may result, for example, from limited sensitivity and specificity of the diagnostic tests involved or from inadequacy of information derived from medical or other records. Another possibility is that we may misclassify a person's exposure status: we may believe the person was exposed when the person was not exposed, or we may believe that the person was not exposed when, in fact, exposure did occur. If exposure data are based on interviews, for example, subjects may either not be aware of their exposure or may erroneously think that it did not occur. It is also possible that research participants may hold back information if they think it might be potentially embarrassing (e.g., giving a history of a sexually transmitted infection or drug use). If ascertainment of exposure is based on old records, data may be lost, incomplete, or inaccurate.

Misclassification may occur in two forms: differential and nondifferential. In *differential misclassification*, the proportion of misclassification differs in different study groups. For example, misclassification of exposure may occur such that unexposed cases are misclassified as being exposed more often than the unexposed controls are misclassified as being exposed. This was seen in the hypothetical example of recall bias (maternal reports of infection during pregnancy and babies born with congenital malformations) presented in the discussion of case-control studies (see Chapter 7). Women who had a baby with a malformation tended to remember (or report) more mild infections that occurred during their pregnancies than mothers of infants without malformations. Controls were probably less likely to remember a mild infection during the pregnancy. Thus, there was a tendency for differential misclassification with regard to prenatal infection, in that more unexposed cases were misclassified as exposed than unexposed controls. A differential misclassification bias can lead either to an apparent association even if one does not really exist or to an apparent lack of association when one does in fact exist.

In contrast, *nondifferential misclassification* results from the degree of inaccuracy that characterizes how information is obtained from any study group—either or both cases and controls or exposed and unexposed persons. Such misclassification is not related to exposure status or to case or control status; it is just a problem inherent in the *data collection methods.* The usual effect of nondifferential misclassification when there are two exposure categories is that the relative risk (RR) or OR tends to be diluted, and it is shifted toward 1.0. In other words, we are less likely to detect an association, even if one really exists. (Note that when there are more than two exposure categories, e.g., light, moderate, and heavy smoking, the shift towards 1.0 may not occur.[14])

This can be seen intuitively. Let's say that in reality there is a strong association of an exposure and a disease—that is, people without the disease have much less exposure than do people with the disease. Unfortunately, by mistake, we have included some diseased persons in our control group (false negatives) and some nondiseased persons in our case group (false positives). We have, in other words, misclassified some of the subjects with regard to diagnosis. In this situation, our controls will not have such a low proportion of exposure because some diseased people have been mistakenly included in this group, and our cases will not have such a high rate of exposure because some nondiseased people have been mistakenly included in the case group.

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BOX 15.1 Some Types and Sources of Information Bias

Bias in abstracting records
Bias in interviewing
Bias from surrogate interviews
Surveillance bias
Recall bias
Reporting bias

As a result, a smaller difference in exposure will be found between our cases and our controls than actually exists between diseased and nondiseased people.

Some of the types and sources of information bias in epidemiologic studies are shown in Box 15.1.

Information bias may be introduced in the way that information is abstracted from medical, employment, or other records, or from the manner in which interviewers ask questions. Bias may also result from *surrogate interviews.* What does this mean? Suppose that we are carrying out a case-control study of pancreatic cancer. The case-fatality from this disease is very high, and the survival time is quite short (median treated survival is under 1 year). When we prepare to interview cases, we find that many of them have died and that many of those who have survived are too ill to be interviewed. We may then approach a family member to obtain information about the case's employment history, diet, and other exposures and characteristics. The person interviewed is most often a spouse or a child. Several problems arise in obtaining information from such surrogates. First, they may not have accurate information about the case's history. A spouse may not know accurately the work-related exposures of the case. Children often know even less than do spouses, especially if the exposures occurred in the participant's childhood. Second, there is evidence that when a wife reports on her husband's work and lifestyle after he dies, she tends to elevate his occupational level and lifestyle factors towards more positive behaviors. She may ascribe to him a higher occupation category than that in which he was actually engaged. She may also convert him posthumously to a nondrinker or nonsmoker, or both.

If a population is monitored over a period of time, disease ascertainment may be better in the monitored population than in the general population, and may introduce a *surveillance bias*, which leads to an erroneous estimate of the RR or OR. For example, some years ago a great deal of interest centered on the possible relationship of oral contraceptive use with thrombophlebitis. It was suggested that physicians monitored patients who had been prescribed oral contraceptives much more closely than they monitored their other patients. As a result, they were more apt to identify cases of thrombophlebitis that developed in those patients who were taking oral contraceptives (and who were therefore being more closely monitored) than among other patients not prescribed oral contraceptives who were therefore not as well monitored. As a result, just through better ascertainment of thrombophlebitis in women receiving oral contraceptives, an apparent association of thrombophlebitis with oral contraceptive use may be observed, even if no true association exists.

In Chapter 7, we discussed *recall bias* in case-control studies. This bias operates to enhance recall in cases compared with controls. Thus, a certain piece of information, such as a potentially relevant exposure, may be recalled by a case but forgotten by a control (as we saw in infection recall among women who had a baby with a congenital malformation). A related type of bias is *reporting bias*, in which a subject may be reluctant to report an exposure he is aware of because of attitudes, beliefs, and perceptions. This has commonly been an issue in HIV/AIDS studies, where risk factors include sexual practices and substance use, which may be subject to significant reporting bias. Methodologic approaches to overcome this bias have been developed to avoid participants from trying to "look good." Audio Computer-Assisted Self-Interviewing (ACASI) was developed to allow study participants to answer sensitive questions to a computer rather than being verbally asked the questions by an interviewer, with some important results.[15,16] If such underreporting is more frequent either among the cases or among the controls, a bias may result. One example is presented below.

The term *wish bias* was coined by Wynder and coworkers[17] to denote the bias introduced by subjects who have developed a disease and who, in attempting to answer the question "Why me?" seek to show, often unintentionally, that the disease is not their fault. Thus, they may deny certain exposures related to lifestyle (such as smoking or drinking); if they are contemplating litigation, they may overemphasize workplace-related exposures. Wish bias can be considered one type of reporting bias.

A point to remember is that *bias is a result of an error in the design or conduct of a study.* Efforts should therefore be made to reduce or eliminate bias or, at the very least, to recognize it and take it into account when interpreting the findings of a study. However, the data needed to document and assess the type and extent of bias may not always be available.

Let's consider an example. The relationship of induced abortion to risk of breast cancer has been a subject of considerable interest in recent years. Although in general no association has been reported for *spontaneous* abortion and risk of breast cancer, the data have been mixed with regard to the possible relationship of *induced* abortion and breast cancer. It was suggested that reporting bias might have played a role in those case-control studies that reported a positive association: healthy controls may have been more reluctant than women with breast cancer to report that they had had an induced abortion.

A study of induced abortion and risk of breast cancer provided an opportunity for the investigators to assess the extent and possible role of such reporting bias, which is one type of information bias. Rookus and van Leeuwen[18] reported a case-control study in the Netherlands in which an overall estimated adjusted RR was 1.9 for induced abortion and breast cancer in parous women. (No association was found in nulliparous women [women who had never been pregnant].) They then compared the findings in two regions of the country—the southeastern region, which has a greater Roman Catholic, more conservative population, and the western region including Amsterdam, which has more liberal attitudes toward abortion. This difference in attitudes is reflected in the fact that the rates of induced abortions in the southeast have always been lower than in the west. As seen in Table 15.2, the authors found the association of induced abortion and breast cancer to be much stronger in the conservative southeast (estimated adjusted RR = 14.6) than in the more liberal west (estimated adjusted RR = 1.3), suggesting that the overall finding of an association of breast cancer and induced abortion in this study was largely attributable to underreporting of abortions by the controls in the southeast. Furthermore, since this study was part of a population-based case-control study of oral contraceptive use and breast cancer risk, it was possible to seek support for the possibility of such an underreporting bias as an explanation for regional differences. In the analysis of reported oral contraceptive use, when women's responses were compared with their physicians' prescriptions, controls in the southeastern region were found to have underreported the duration of their oral contraceptive use by more than 6 months more than controls in the western region.

TABLE 15.2 Relative Risks[a] (RR) and 95% Confidence Intervals (CI) of the Development of Breast Cancer at Ages 20 to 45 Years in Relation to Previous Induced Abortions Reported by Parous Women in All Regions and in Western and Southeastern Regions of the Netherlands

	Unadjusted RR	Adjusted RR[b]	95% CI
All regions	1.8	1.9	1.1–3.2
Western region	1.2	1.3	0.7–2.6
Southeastern region	12.3	14.6	1.8–120

[a]Relative risks estimated using conditional logistic regression methods for matched pairs.
[b]Adjusted for spontaneous or induced abortion, age at first full-term pregnancy, number of full-term pregnancies, weeks of breast-feeding, family history of breast cancer, and use of injectable contraceptives.
Modified from Rookus MA, van Leeuwen FE. Induced abortion and risk for breast cancer: reporting (recall) bias in a Dutch case-control study. *J Natl Cancer Inst.* 1996;88:1759–1764.

Even location of the interview may influence the truthfulness of the information provided by the study subjects. D'Avanzo and her colleagues found different proportions of reported alcohol consumption when interviewing patients in the hospital and then again at home: when interviewed in the hospital, 62% claimed to be drinkers, but 72% reported they were drinkers upon subsequent home interviews.[19]

CONFOUNDING

A problem posed in many epidemiologic studies is that we observe a true association and are tempted to suggest a causal inference when, in fact, the relationship may not be causal. This brings us to the subject of *confounding*, one of the most important problems in observational epidemiologic studies.

What do we mean by *confounding*? In a study of whether exposure A is a cause of disease B, we say that

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a third factor, factor X, is a confounder *if the following are true*:

1. Factor X is a known risk factor for disease B.
2. Factor X is associated with exposure A, but is not a result of exposure A.

Recall the example we discussed in Chapter 7 of the relationship between coffee and cancer of the pancreas. Smoking was a confounder, because although we were interested in a possible relationship between coffee drinking (exposure A) and pancreatic cancer (disease B), the following are true of smoking (factor X):

1. Smoking is a known risk factor for pancreatic cancer.
2. Smoking is associated with coffee drinking but is not a result of coffee drinking.

Thus if an association is observed between coffee drinking and cancer of the pancreas, it may be (1) that coffee actually causes cancer of the pancreas, or (2) that the observed association of coffee drinking and cancer of the pancreas may be a result of confounding by cigarette smoking (i.e., we observe the association of coffee drinking and pancreatic cancer because cigarette smoking is a risk factor for pancreatic cancer and cigarette smoking is associated with coffee drinking; Fig. 15.1).

When we observe an association, we ask whether it is causal (see Fig. 15.1A) or whether it is a result of confounding by a third factor that is both a risk factor for the disease and is associated with the putative exposure in question (see Fig. 15.1B).

Let's look at a hypothetical example: Table 15.3 shows data from an unmatched case-control study of an exposure and a disease, in which 100 cases and 100 controls were studied.

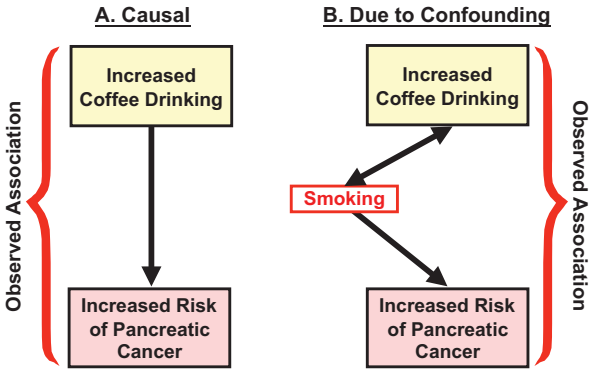

Fig. 15.1 The association between increased coffee drinking and increased risk of pancreatic cancer.

TABLE 15.3 Hypothetical Example of Confounding in an Unmatched Case-Control Study: I. Numbers of Exposed and Nonexposed Cases and Controls

Exposed	Cases	Controls
Yes	30	18
No	70	82
Total	100	100

$$\text{Odds ratio} = \frac{30 \times 82}{70 \times 18} = 1.95$$

TABLE 15.4 Hypothetical Example of Confounding in an Unmatched Case-Control Study: II. Distribution of Cases and Controls by Age

Age (yr)	Cases	Controls
<40	50	80
≥40	50	20
Total	100	100

We calculate an unmatched OR of 1.95. The question arises: Is this association of the exposure with the disease a causal one, or could it have resulted from differences in the age distributions of the cases and controls? In other words, is the observed relationship confounded by age? The first question to ask in addressing this issue is whether age is related to being a case or a control. This question is answered by the analysis in Table 15.4.

We see that 80% of the controls are younger than 40 years of age, compared with only 50% of the cases. Thus, older age is associated with being a case (having the disease), and younger age is associated with being a control (not having the disease).

The next question is whether age is related to exposure status.

Table 15.5 looks at the relationship of age to exposure for all 200 subjects studied, regardless of their case-control status. We see that 130 people were younger than 40 years (the 50 + 80 in the top row of Table 15.4), and of these, 13 (10%) were exposed. Among the 70 subjects who were older than 40 years, 35 (50%) were exposed. Thus, age is clearly related to exposure. So, at this point, we know that age is related to being a case

TABLE 15.5 Hypothetical Example of Confounding in an Unmatched Case-Control Study: III. Relationship of Exposure to Age

Age (yr)	Total	Exposed	Not Exposed	% Exposed
<40	130	13	117	10
≥40	70	35	35	50

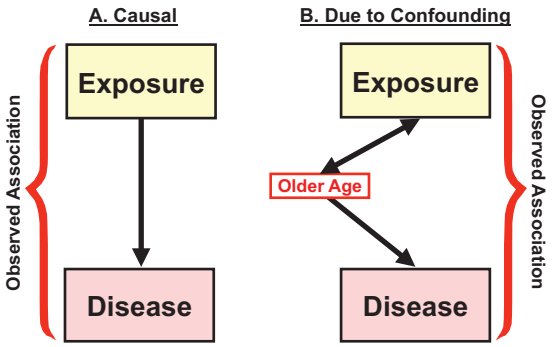

Fig. 15.2 Schematic representation of the issue of potential confounding.

TABLE 15.6 Hypothetical Example of Confounding in an Unmatched Case-Control Study: IV. Calculations of Odds Ratios After Stratifying by Age

Age (yr)	Exposed	Cases	Controls	Odds Ratio
<40	Yes	5	8	$\frac{5 \times 72}{45 \times 8} = \frac{360}{360} = 1.0$
	No	45	72	
	Totals	**50**	**80**	
≥40	Yes	25	10	$\frac{25 \times 10}{25 \times 10} = \frac{250}{250} = 1.0$
	No	25	10	
	Totals	**50**	**20**	

BOX 15.2 Approaches to Handling Confounding

In designing and carrying out the study:
1. Individual matching
2. Group matching

In the analysis of data:
1. Stratification
2. Adjustment

(the cases were older than the controls); we also know that being exposed is related to older age.

As shown in Fig. 15.2, the question is: Is the association of exposure and disease causal (see Fig. 15.2A), or could we be seeing an association of exposure with disease only because there is an age difference between cases and controls, and older age is also related to being exposed (see Fig. 15.2B)? In other words, does exposure cause the disease, or is the observed association between the exposure and disease a result of confounding by a third factor (in this case, age)?

How can we clarify this issue? One approach is seen in Table 15.6. We can carry out a stratified analysis with subjects in two age groups: younger than 40 years and older than 40 years. Within each stratum a 2×2 table is created, and an OR is calculated for each. When we calculate the OR separately for the younger and the older subjects, we find the OR to be 1.0 in each stratum. Thus, the only reason we originally had an OR of 1.95 in Table 15.3 was because there was a difference in age distributions between the cases and the controls. We therefore conclude, in this example that age is a confounder.

How can we address the problem of confounding? As seen in Box 15.2, the issue of confounding can be addressed either in designing and carrying out a study or in analysis of the data. In *designing and carrying out a case-control study*, we can match the cases to the controls, as discussed in Chapter 7 (by either group matching or individual matching), for the factor that we suspect could be a possible confounder. In this example, we could match by age to eliminate any age difference between the cases and the controls. If, after matching in this way, we then observe an association of exposure and disease, we would know that we could not attribute the observed association to age differences in cases and controls.

Alternatively, we can handle the problem of confounding in the *data analysis* in one of two ways: stratification or adjustment. Let's briefly discuss stratification, which was just demonstrated in the hypothetical example (see Table 15.6). Say we are interested in the relationship of smoking and lung cancer. We want to know whether the observed higher risks of lung cancer in smokers could be the result of confounding by air

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TABLE 15.7 An Example of Stratification: Lung Cancer Rates by Smoking Status and Degree of Urbanization

	CANCER RATES	
Degree of Urbanization	Nonsmokers	Smokers
None		
Slight		
Town		
City		
Totals		

pollution and/or urbanization. Perhaps we are observing a relationship of smoking and lung cancer not because smoking causes lung cancer, but because air pollution causes lung cancer and smoking is more frequent in polluted areas (such as urban areas). Perhaps smoking is more common in cities than in rural areas.

How can we address this question? One approach would be to stratify the data by degree of urbanization—rural, town, or major city. We could then calculate the lung cancer rates in smokers and nonsmokers in each urbanization stratum (Table 15.7).

If the relationship of lung cancer to smoking is due to smoking, and not to the confounding effect of pollution and/or urbanization, then *in each stratum of urbanization* the incidence of lung cancer should be higher in smokers than in nonsmokers. It would then be clear that the observed association of smoking and lung cancer could not be due to degree of urbanization.

We may prefer not just to dichotomize smoking groups into smokers and nonsmokers, but also to include in the analysis the number of cigarettes smoked per day (which of course is subject to some error, being estimated by study participants).

In Table 15.8, we have expanded cigarette smoking into categories of amount subjects said that they smoked per day. Again, we can calculate the incidence in each cell of the table. If the observed association of cigarette smoking and lung cancer is not due to confounding by urbanization or pollution or both, we would expect to see a dose-response pattern *in each stratum of urbanization.*

Fig. 15.3 shows actual age-adjusted lung cancer mortality rates per 100,000 person-years by urban-rural classification and smoking category in one of the classic epidemiologic reports on smoking and lung cancer mortality. For each degree of urbanization, lung cancer mortality rates in smokers are shown by the blue bars, and nonsmoker mortality rates are indicated by light green bars. We see that in every level (or stratum) of urbanization, lung cancer mortality is higher in smokers than in nonsmokers. Therefore, the observed association of smoking and lung cancer cannot be attributed to level of urbanization. By examining each stratum separately, we are, in effect, holding urbanization constant, and we still find much higher lung cancer mortality in smokers than in nonsmokers.

At the same time, it is interesting to examine the data for nonsmokers (shown by the green bars). If we draw a line connecting the tops of these bars, we see that the higher the urbanization level, the higher the incidence of lung cancer in nonsmokers (Fig. 15.4). Thus, there is a dose-response relationship of lung cancer and urbanization in nonsmokers. However, as we have seen, this relationship cannot explain the association of lung

TABLE 15.8 An Example of Further Stratification: Lung Cancer Rates by Smoking Level and Degree of Urbanization

	CANCER RATES			
		SMOKERS		
Degree of Urbanization	Nonsmokers	<1 Pack/Day	1 Pack/Day	>1 Packs/Day
None				
Slight				
Town				
City				
Totals				

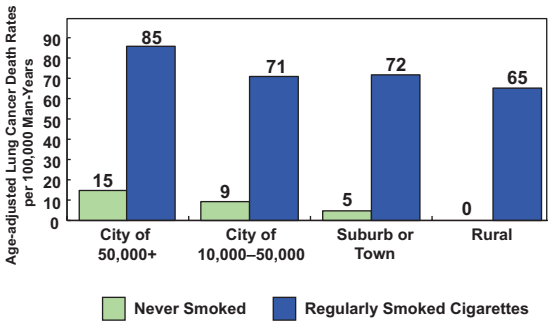

Fig. 15.3 Age-adjusted lung cancer death rates per 100,000 person-years by urban-rural classification and by smoking category. (Modified from Hammond EC, Horn D. Smoking and death rates: report on 44 months of follow-up of 187,783 men: II. Death rates by cause. *JAMA*. 1958;166:1294–1308. Copyright 1958, American Medical Association.)

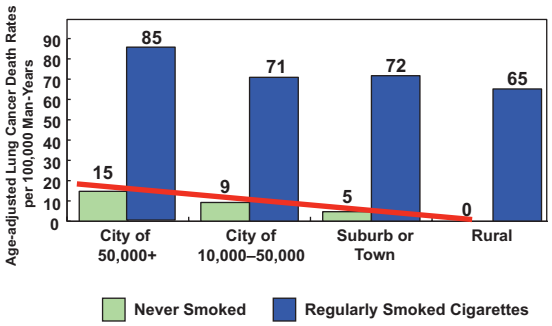

Fig. 15.4 Relationship of degree of urbanization to lung cancer death rates in nonsmokers. The *sloping line* connects the age-adjusted lung cancer death rates per 100,000 person-years by urban-rural classification in nonsmokers. (Modified from Hammond EC, Horn D. Smoking and death rates: report on 44 months of follow-up of 187,783 men: II. Death rates by cause. *JAMA*. 1958;166:1294–1308. Copyright 1958, American Medical Association.)

cancer with smoking, as the latter relationship holds within each level of urbanization.

Fig. 15.5 shows the relationship among smoking, drinking, and cancer of the esophagus. Four strata (levels) of the amount smoked are shown. Within each smoking stratum, the risk of esophageal cancer is plotted in relation to the amount of alcohol consumed.

What do we observe? The more a person reports smoking, the higher the levels of esophageal cancer. However, within each stratum of smoking, there is a dose-response relationship of esophageal cancer and the amount of alcohol consumed. Therefore, we cannot

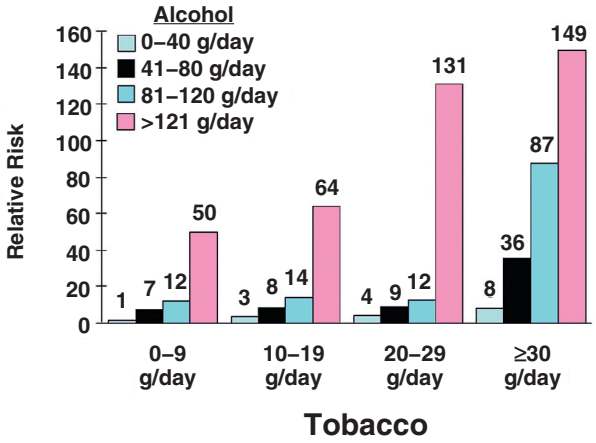

Fig. 15.5 Relative risk of developing cancer of the esophagus in relation to smoking and drinking habits. (Modified from Tuyns AJ, Pequignot G, Jensen OM. Esophageal cancer in Ille-et-Vilaine in relation to levels of alcohol and tobacco consumption: risks are multiplying. *Bull Cancer*. 1977;64:45–60.)

attribute to smoking the effects of alcohol consumption on esophageal cancer. Instead, both smoking and alcohol have separate effects on the risk of esophageal cancer.

It is important to note that in this presentation of data, we cannot compare smokers with nonsmokers or drinkers with nondrinkers because the authors have pooled the group that smokes 0 to 9 g of tobacco per day, and they have also pooled nondrinkers with minimal drinkers. Therefore we have no rates for persons who are truly *unexposed* to alcohol or tobacco. It would have been preferable to have kept the data for unexposed persons separate so that RRs could have been calculated based on rates in unexposed persons. Mixing nondrinkers with light drinkers and nonsmokers with light smokers makes it difficult to properly analyze the data.

Two final points on confounding: First, when we identify a confounder, we generally consider it a problem and want to find ways to address the issue of confounding. However, sometimes finding a confounded relationship can also be enlightening. Even if an apparent association between exposure A (the factor in which we are primarily interested) and disease B is actually due to some third confounding factor X, so that exposure A is not causally related to disease B, screening for exposure A can nevertheless be useful because it permits us to identify people who are at elevated risk for the

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disease and direct appropriate preventive and therapeutic interventions to them. Thus, a confounded relationship may still be a helpful guide in screening populations even when we do not identify the specific etiologic agent involved.

Second, confounding is not an error in the study, but rather it is a true phenomenon that is identified in a study and must be understood. Bias is a result of an error in the way that the study has been carried out, but confounding is a valid finding that describes the nature of the relationship among several factors and the risk of disease. However, *failure to take confounding into account in interpreting the results of a study* is indeed an error in the conduct of the study and can bias the conclusions of the study. In other words, a confounded association may be useful to define a high-risk group, even if the association is not causal.

INTERACTION

To this point, our discussion has generally assumed the presence of a single exposure (risk factor) in the etiology of a disease. Although this approach is useful for discussion purposes, in real life, we rarely deal with single causes. In the previous examples of the relationship of lung cancer to smoking and urbanization and the relationship of esophageal cancer to drinking and smoking, we have already seen more than one factor involved in disease etiology. In this section, we ask the question: How do multiple factors interact in causing disease?

What do we mean by *interaction*? MacMahon[20] defined interaction as follows: "*When the incidence rate of disease in the presence of two or more risk factors differs from the incidence rate expected to result from their individual effects.*" The effect can be greater than what we would expect (positive interaction, synergism) or less than what we would *expect* (negative interaction, antagonism). The problem is to determine what we would expect to result from the individual effects of the exposures. Interaction is sometimes referred to as *effect modification,* although in some situations these are different phenomena.[21] (A discussion of the difference between interaction and effect modification is beyond the scope of this introductory textbook.)

Fig. 15.6 shows an algorithm for exploring the possibility of interaction.

In examining our data, the first question is whether an association has been observed between the exposure in question and disease. If so, is it due to confounding? If we decide that it is *not* due to confounding—that is, the association is causal—then we ask whether the association is equally strong in each of the strata that are formed on the basis of some third variable. For example, is the association between smoking and lung cancer equally strong in strata formed on the basis of the degree of urbanization? If the association is equally strong in all strata, there is no interaction. But if the association is of different strengths in different strata formed on the basis of age, for example (if the association is stronger in older people than in younger people), an interaction has been observed between age and exposure in producing the disease. If there was no interaction, we would expect the association to be of the same strength in each stratum.

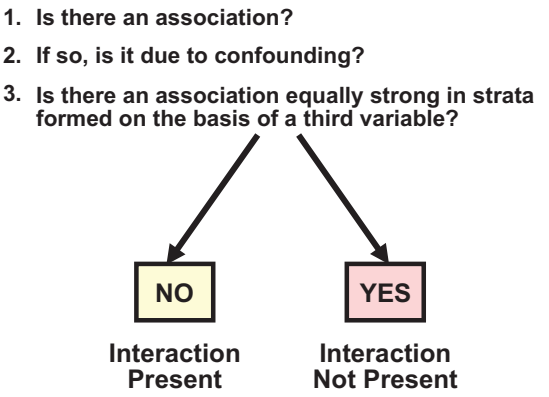

Fig. 15.6 Questions to ask regarding the nature of the relationship between exposure and outcome.

Let's look more closely at interaction. Table 15.9 shows the incidence in persons exposed to either one of two risk factors (A or B), to both factors, or to neither factor, in a hypothetical example.

TABLE 15.9 Incidence Rates for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data)

		Factor A: −	Factor A: +
Factor B	−	3.0	9.0
Factor B	+	15.0	

In persons with neither exposure, the incidence is 3.0. In persons exposed to factor A only and not to factor B, the incidence is 9.0. In persons exposed to factor B only and not to factor A, the incidence is 15.0. These are the individual effects of each factor considered separately.

What would we expect the incidence to be in persons who are exposed to both factors A and B (the lower right-hand cell in Table 15.9) if those people experienced the risk resulting from the independent contributions of both factors? The answer depends on the type of model that we propose. Let's assume that when there are two exposures, the effect of one exposure is *added* to the effect of the second exposure—that is, the model is *additive*. What, then, would we expect to see in the lower right-hand cell of the table? Let's use as an example the people who have neither exposure, whose risk in the absence of both exposures is 3.0. How does exposure to factor A affect their risk? It adds 6.0 to the 3.0 to produce a risk of 9.0. If factor A adds a risk of 6.0 to the risk that exists without factor A, it should have the same effect both in people exposed to factor B and in those not exposed to factor B. Because factor A adds 6.0 to the 3.0, it would also be expected to add 6.0 to the 15.0 rate of people exposed to factor B when they have exposure to A added as well. Thus, we would expect the effects of exposures to both factors to yield an incidence of 21.0.

We can also view this as follows: If factor B adds 12.0 to the 3.0 incidence of people with neither exposure, we would expect it to add 12.0 to any group, including the group exposed only to factor A, whose incidence is 9.0. Therefore, the effect of exposure to both A and B would be expected to equal 9.0 added to 12.0, or 21.0. (Remember that the 3.0 is a background risk that is present in the absence of both A and B. When we calculate the combined effect of factors A and B, we cannot just add 9.0 and 15.0—we must be sure that we do not count the background risk [3.0] twice.) The left-hand side of Table 15.10 shows the completed table from the partial data presented in Table 15.9.

Recall that when we discuss differences in risks, we are talking about *attributable risks*. This is shown on the right side of Table 15.10. If we examine persons who have neither exposure, they have a background risk, but the attributable risk—that is, the risk attributable to exposure to factor A or B—is 0. As stated earlier, exposure only to factor A adds 6, and exposure only to factor B adds 12. What will the attributable risk be for both exposures? The answer is 18—that is, 18 more than the background risk. The additive model is summarized in Table 15.11. An additive model is based on absolute differences (attributable risk in the exposed).

What if an additive model does not correctly describe the effect of exposure to two independent factors? Perhaps a second exposure does not *add* to the effect of the first exposure but instead *multiplies* the effect of the first exposure. If having a certain exposure doubles a person's risk, we might expect it to double that risk regardless of whether that person had another exposure. For example, if the effect of alcohol is to double a person's risk for a specified cancer being investigated, we might expect it to double that risk for both smokers and nonsmokers. The appropriate model for the effects of

TABLE 15.10 Incidence Rates and Attributable Risks for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data in an Additive Model: I)

		Incidence Rates		Attributable Risks	
		Factor A		Factor A	
		−	+	−	+
Factor B	−	3.0	9.0	0	6
	+	15.0	21.0	12	

TABLE 15.11 Incidence Rates and Attributable Risks for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data in an Additive Model: II)

		Incidence Rates		Attributable Risks	
		Factor A		Factor A	
		−	+	−	+
Factor B	−	3.0	9.0	0	6
	+	15.0	21.0	12	18

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TABLE 15.12 Incidence Rates for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data)

Factor B	Factor A: −	Factor A: +
−	3.0	9.0
+	15.0	

TABLE 15.13 Incidence Rates and Relative Risks for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data in a Multiplicative Model: I)

	Incidence Rates		Relative Risks	
	Factor A: −	Factor A: +	Factor A: −	Factor A: +
Factor B: −	3.0	9.0	1	3
Factor B: +	15.0	45.0	5	

two independent factors might therefore be a *multiplicative* rather than an additive model.

Let's return to our original data on risk resulting from neither exposure, or from exposure to factor A or B. These data are shown again in Table 15.12.

We see that exposure to factor A triples the risk, compared with that seen when factor A is absent (9.0 compared with 3.0). What would we therefore expect to find in the lower right-hand cell of the table when both exposures are present? Since in the absence of factor B, factor A has tripled the risk of 3.0, we would also expect it to triple the risk of 15.0 observed when exposure to factor B is present. If so, the effect from exposure to both factors would be 45.0. Again, we can calculate this in a different fashion. Factor B multiplies the risk by 5 (15.0 compared with 3.0) when factor A is absent. We would therefore expect it to have the same effect when factor A is present. Because the risk when factor A is present is 9.0, we would expect the presence of factor B to yield a risk of 45.0 (9.0 × 5; Table 15.13).

TABLE 15.14 Incidence Rates and Relative Risks for Groups Exposed to Neither Risk Factor or to One or Two Risk Factors (Hypothetical Data in a Multiplicative Model: II)

	Incidence Rates		Relative Risks	
	Factor A: −	Factor A: +	Factor A: −	Factor A: +
Factor B: −	3.0	9.0	1	3
Factor B: +	15.0	45.0	5	15

The left-hand side of Table 15.13 shows the completed incidence rate table. A multiplicative model is based on ratio-based measures of association (e.g., relative risk, odds ratio). This is shown on the right-hand side of the table. What value would we expect to find in the blank cell?

If we now assign the background risk (3.0) a value of 1, against which to compare the other values in the table, exposure to factor A triples the risk, yielding an RR of 3 for factor A in the absence of factor B. Factor B multiplies the risk by 5, yielding an RR of 5 for exposure to factor B in the absence of factor A. When both factors A and B are operating, we would expect to see an RR of 15 (45.0/3.0) as seen on the left or 3 × 5 as seen on the right in Table 15.14.

We have considered two models thus far: additive and multiplicative. Several questions remain: What would we expect to see for the independent effects of two risk factors? Do we expect an additive model or a multiplicative model?

The answers may not be obvious. If two factors are operating and the incidence is 21.0, the result is consistent with an additive model. If the incidence is 45.0, the result is consistent with a multiplicative model. However, if the incidence resulting from two factors is 60.0, for example, even the value for a multiplicative model is clearly exceeded, and interaction is present—that is, an effect greater than would be expected from the independent effects of the two separate factors.

However, if the incidence is 30.0, it is less than expected from a multiplicative model but still more than

TABLE 15.15 Deaths From Lung Cancer (Per 100,000) Among Individuals With and Without Exposure to Cigarette Smoking and Asbestos

	ASBESTOS EXPOSURE	
Cigarette Smoking	No	Yes
No	11.3	58.4
Yes	122.6	601.6

Modified from Hammond EC, Selikoff IJ, Seidman H. Asbestos exposure, cigarette smoking and death rates. *Ann NY Acad Sci.* 1979;330:473–490.

TABLE 15.16 Relative Risks[a] of Oral Cancer According to Presence or Absence of Two Exposures: Smoking and Alcohol Consumption

		Smoking	
		No	Yes
Alcohol	No	1.00	1.53
	Yes	1.23	5.71

[a]Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank alcohol.
From Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis.* 1972;25:711–716.

TABLE 15.17 Risk Ratios[a] for Oral Cancer According to Level of Exposure to Alcohol and Smoking: I

Alcohol Consumption (oz/day)	CIGARETTE EQUIVALENTS PER DAY			
	0	<20	20–39	≥40
0	1.00	1.52	1.43	2.43
<0.4	0.40	1.67	3.18	3.25
0.4–1.5	1.60	4.36	4.46	8.21
>1.5	2.33	4.13	9.59	15.50

[a]Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank.
From Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis.* 1972;25:711–716.

expected from an additive model. Then we would ask, "Is this more than we would expect from the independent effects of the two factors?" It is difficult to know the answer without more information about the biology of the disease, the mechanisms involved in the pathogenesis of the disease, and how such factors operate at cellular and molecular levels. Most experts accept any effect greater than additive as evidence of positive interaction, which is also called *synergism*. However, this opinion is often based on statistical considerations, whereas the validity of the model should ideally be based on biological knowledge. The model may differ from one disease to another and from one exposure to another.

Let's consider a few examples. In a cohort study of smoking and lung cancer, Hammond and colleagues[22] studied the risk of lung cancer in 17,800 asbestos workers in the United States and in 73,763 men who were not exposed to asbestos in relation to their smoking habits. Table 15.15 shows the findings for deaths from lung cancer in relation to exposure. If the relationship between smoking and asbestos exposure were additive, we would expect the risk in those exposed to both smoking and asbestos (the lower right-hand cell) to be 58.4 + 122.6 − 11.3, or 169.7 (recall that the 11.3 background risk is subtracted to avoid counting it twice). Clearly, the observed value of 601.6 is much greater than the expected additive value. In fact, the data in Table 15.15 closely approximate a multiplicative model and strongly suggest synergism between asbestos exposure and tobacco smoking.

A second example is seen in Table 15.16, which shows the RR of oral cancer by presence or absence of two exposures: smoking and alcohol consumption. The risk is set at 1.00 for persons with neither exposure. Is there evidence of an interaction? What would we expect the risk to be if the effect were multiplicative? We would expect 1.53 × 1.23, or 1.88. Clearly the observed effect of 5.71 is higher than a multiplicative effect and indicates the presence of interaction.

Let's look at more detailed data for these relationships using dose data for alcohol consumption and for smoking (Table 15.17).

Again, the risk in those who do not drink and do not smoke is set at 1.0. In those with the highest level of alcohol consumption and the highest level of smoking, the risk is 15.50. Is an interaction evident? The data

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TABLE 15.18 Risk Ratios[a] for Oral Cancer According to Level of Exposure to Alcohol and Smoking: II

Alcohol Consumption (oz/day)	CIGARETTE EQUIVALENTS PER DAY		
	0	<20	20–39
None	1.00	1.52	1.43
<0.4	0.40	1.67	3.18
0.4–1.5	1.60	4.36	4.46

[a]Risks are expressed relative to a risk of 1.00 for persons who neither smoked nor drank.

From Rothman K, Keller A. The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. *J Chronic Dis*. 1972;25:711–716.

TABLE 15.19 Relative Risks of Lung Cancer According to Smoking and Radiation Exposure in Two Populations

Radiation Level	URANIUM WORKERS (SMOKING LEVEL)		A-BOMB SURVIVORS (SMOKING LEVEL)	
	Low	High	Low	High
Low	1.0	7.7	1.0	9.7
High	18.2	146.8	6.2	14.2

From Blot WJ, Akiba S, Kato H. Ionizing radiation and lung cancer: a review including preliminary results from a case-control study among A-bomb survivors. In: Prentice RL, Thompson DJ, eds. *Atomic Bomb Survivor Data: Utilization and Analysis*. Philadelphia: Society for Industrial and Applied Mathematics; 1984:235–248.

appear to support this. The highest values in smokers who are nondrinkers and in drinkers who are nonsmokers are 2.43 and 2.33, respectively; the value of 15.5 clearly exceeds the resulting product of 5.66 which would be expected with a multiplicative effect.

However, a problem with these data should be mentioned. Note that each category of smoking or drinking has upper and lower boundaries, except for the highest categories, which have no upper boundaries. Therefore, the high risk of 15.50 could result from the presence of a few extreme outliers—either extraordinarily heavy smokers or extraordinarily heavy drinkers.

Is there a way to avoid this problem and still use the data shown here? We could ignore the right-hand column and the bottom row and look only at the resulting 3×3 table (Table 15.18). Now all the categories have both upper and lower boundaries. If the model were multiplicative, we would expect to see 1.43×1.60, or 2.29, rather than the 4.46 that was observed. Thus, we still see evidence of interaction, but much weaker evidence than we had seen in the full table, with its indefinite high-exposure categories. This suggests that the problem of the lack of upper boundaries of categories was indeed a contributor to the high value of 15.50 seen in the 4×4 table.

As we have said, the decision as to whether an additive model or a multiplicative model is most relevant in a given situation should depend on the biology of the disease. Table 15.19 shows data regarding the risks of cancer from radiation and smoking in two different populations: uranium workers (left) and survivors of the 1945 atomic bombing of Japan (right). Low and high levels of smoking and low and high levels of radiation are shown for both groups in Table 15.19.

What kind of model is suggested in Table 15.19? Clearly, a multiplicative relationship is suggested; 146.8 is close to the product of 7.7×18.2 (140.1). The columns on the right suggest an additive model; 14.2 is close to the sum of $9.7 + 6.2 - 1.0$ (14.9). Therefore, although the data address radiation and smoking in two populations, in one setting, the exposures relate in an additive way, and in the other, they relate in a multiplicative way. It is not known whether this is a result of differences in radiation exposure in uranium mines compared with that from atomic bombs. Such a hypothesis is not unreasonable; we know that there was even a difference in the radiation emitted by the atomic bombs at Hiroshima and Nagasaki and that the dose-response curves for cancer were different in the two cities. Further, the location of survivors in each city may have varied. In any case, the fact that two exposures that are ostensibly the same (or, at least, similar) may have different interrelationships in different settings is an intriguing observation that requires further exploration.

Finally, a dramatic example of interaction is seen in the relationship between aflatoxin and chronic hepatitis B infection to the risk of liver cancer (Table 15.20). In this Chinese study, hepatitis B infection alone multiplied the risk of liver cancer by 7.3; aflatoxin exposure alone multiplied the risk by 3.4. However, when both exposures were present, the RR rose to 59.4, far in excess of what we might expect in both an additive and a

TABLE 15.20 Risks[a] of Liver Cancer for Persons Exposed to Aflatoxin or Chronic Hepatitis B Infection: An Example of Interaction

	Aflatoxin-Negative	Aflatoxin-Positive
HBsAg negative	1.0	3.4
HBsAg positive	7.3	59.4

[a]Adjusted for cigarette smoking.
HBsAg, Hepatitis B surface antigen.
Modified from Qian GS, Ross RK, Yu MC, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev*. 1994;3:3–10.

multiplicative model.[a] Such an observation of synergy is of major clinical and public health interest, but also suggests important directions for further laboratory research into the etiology and pathogenesis of liver cancer.

When translation of an association to policy is suggested, additive interaction is more relevant. For example, in the Atherosclerosis Risk in Communities (ARIC) cohort study, the coronary heart disease rate ratio was much higher for women than for men. However, the absolute differences, defining absence of additive interaction, were the same. This finding suggested that, from the prevention viewpoint, it would be as important to focus on women as on men as high risk groups.[23] The finding of an additive interaction or synergism may therefore have practical policy implications involving issues such as who is responsible for a disease and who should pay compensation to the victims. For example, earlier in this chapter, we discussed the relationship between smoking and asbestos exposure in producing cancer, a relationship that clearly is strongly interactive or synergistic. Litigation against asbestos manufacturers dates back at least to the 1970s, and large awards were made by the courts. In 1998, at a time of increasing legal actions against the tobacco companies, a coalition of some of the victims of asbestos exposure joined forces with asbestos manufacturers to demand that Congress set aside a large amount of money from any national tobacco settlement bill to compensate people whose cancer was caused by the combined exposure to both asbestos and tobacco, a claim they justified by pointing to the synergistic relationship of these exposures. Those who objected to this demand claimed that those making the demand were in effect freeing the asbestos manufacturers from paying their obligation (shifting it to tobacco manufacturers) and were doing so only because they believed that it might be easier to obtain significantly higher compensation from tobacco companies than from asbestos manufacturers. In so doing, they were willing to forge an alliance with asbestos manufacturers who had previously been found responsible for their disease. The basis for this approach was the well-documented synergy of asbestos and tobacco smoking in causing cancer.

[a]A simple formula to calculate additive expected joint relative risk (RR) or odds ratio (OR) is [RR or OR for the isolated effect of factor A] + [RR or OR for the isolated effect of factor B] − 1.0. In the example, the additive expected joint RR is 7.3 + 3.4 − 1.0 = 9.7, which is much lower than the observed RR of 59.4, thus defining a strong additive interaction. (This approach is particularly useful in case-control studies, in which absolute differences in rates are not available.) The formula for the multiplicative expected joint RR or OR is based on multiplying the independent RRs or ORs; in the example, 7.3 × 3.4 = 24.8, which is also much lower than the observed RR of 59.4. Thus, it can be concluded that there are both additive and multiplicative interactions.

CONCLUSION

This chapter has reviewed the concepts of bias, confounding, and interaction in relation to the derivation of causal inferences from epidemiological studies. Biases reflect inadequacies in the design or conduct of a study, and clearly affect the validity of the findings. Biases, therefore, need to be assessed and, if possible, eliminated. Confounding and interaction, on the other hand, describe the reality of the interrelationships between certain exposures and a certain disease outcome. Confounding and interaction characterize virtually every situation in which etiology is addressed because most causal questions involve the relationships of multiple exposures and multiple, possibly etiologic, factors. While confounding is a problem that needs to be addressed at the study design or analysis stage, interaction is an important phenomenon that we should prespecify (preferably) and report. Such relationships are particularly important in investigating the roles of genetic and environmental factors in disease causation and in assigning responsibility for adverse health outcomes from environmental exposures. Assessing the relative contributions of genetic and environmental factors is discussed in the following chapter.

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REVIEW QUESTIONS FOR CHAPTER 15

1. *Which of the following is an approach to handling confounding?*
- **a.** Individual matching
- **b.** Stratification
- **c.** Group matching
- **d.** Adjustment
- **e.** All of the above

2. *Which of the following approaches can handle confounding at the design stage of the study?*
- **a.** Stratification
- **b.** Adjustment
- **c.** Restriction
- **d.** Regression

3. *It has been suggested that physicians may examine women who use oral contraceptives more often or more thoroughly than women who do not. If so, and if an association is observed between phlebitis and oral contraceptive use, the association may be due to:*
- **a.** Selection bias
- **b.** Interviewer bias
- **c.** Surveillance bias

d. Nonresponse bias
e. Recall bias

Questions 4 through 7 are based on the information given below:

		Factor A: −	Factor A: +
Factor B	−	3	7
	+	8	

4. *Fill in the blank cell in the first table using the additive model of interaction:* _____
5. *Fill in the blank cell in the first table using the multiplicative model of interaction:* _____

Convert the numbers in the above table to attributable risks for the additive model (below, left) and relative risks for the multiplicative model (below, right).

ADDITIVE MODEL

		Factor A: −	Factor A: +
Factor B	−	0	
	+		

MULTIPLICATIVE MODEL

		Factor A: −	Factor A: +
Factor B	−	1	
	+		

6. *Fill in the bottom right cell of the table at the bottom of the left column for the attributable risk of having both factors A and B (additive model):* _____
7. *Fill in the bottom right cell of the table at the bottom of the left column for the relative risk of having both factors A and B (multiplicative model):* _____

Question 8 is based on the information given below:

In a case-control study of the relationship of radiation exposure and thyroid cancer, 50 cases admitted for thyroid cancer and 100 "controls" admitted during the same period for treatment of hernias were studied. Only the cases were interviewed, and 20 of the cases were found to have been exposed to x-ray therapy in the past, based on the interviews and medical records. The controls were not interviewed, but a review of their hospital records when they were admitted for hernia surgery revealed that only two controls had been exposed to x-ray therapy in the past.

8. *Based on the description given above, what source of bias is* least likely *to be present in this study?*
   a. Recall bias
   b. Bias due to controls being nonrepresentative of the nondiseased population
   c. Bias due to use of different methods of ascertainment of exposure in the cases and controls
   d. Bias due to loss of subjects from the control group over time
   e. Selection bias for exposure to x-ray therapy in the past
9. *In 1990, a case-control study was conducted to investigate the positive association between artificial sweetener use and bladder cancer. Controls were selected from a hospital sample of patients diagnosed with obesity-related conditions. Obesity-related conditions have been positively associated with artificial sweetener use. How would the use of these patients as controls affect the estimate of the association between artificial sweetener use and bladder cancer?*
   a. The estimate of association would accurately reflect the true association regardless of the association between artificial sweetener use and obesity-related conditions
   b. The estimate of association would tend to underestimate the true association
   c. More information is needed on the strength of association between artificial sweetener use and obesity-related conditions before any judgment can be made
   d. The estimate of association would tend to overestimate the true association
   e. More information is needed on the strength of association between artificial sweetener use and bladder cancer before any judgment can be made

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16

Identifying the Roles of Genetic and Environmental Factors in Disease Causation

To produce another Wolfgang Amadeus Mozart, we would need not only Wolfgang's genome but his mother's uterus, his father's music lessons, his parents' friends and his own, the state of music in 18th century Austria, Haydn's patronage, and on and on, in ever-widening circles. Without Mozart's set of genes, the rest would not suffice; there was, after all, only one Wolfgang Amadeus Mozart. But we have no right to the converse assumption: that his genome, cultivated in another world at another time, would result in the same musical genius. If a particular strain of wheat yields different harvests under different conditions of climate, soil, and cultivation, how can we assume that so much more complex a genome as that of a human being would yield its desired crop of operas, symphonies, and chamber music under different circumstances of nurture?[1]

—Leon Eisenberg, MD, DSc, child psychiatrist, social psychiatrist, and medical educator (1922–2009)

LEARNING OBJECTIVES

- To examine how epidemiologic study designs can clarify the roles of genetic and environmental factors in risk of disease and their possible interactions.
- To show how genetic markers are used to map genes controlling risk of different diseases, including complex diseases.
- To test for interaction between genes and environmental risk factors.
- To discuss how innovative epidemiologic and molecular biology methods can help to define the etiologic roles of environmental and genetic risk factors, and potentially permit development of individualized treatments of disease.

In previous chapters, we discussed study designs for identifying causes of disease focused primarily on the etiologic role of environmental factors. However, to prevent disease, we must simultaneously consider both host genetic factors and environmental factors. Human beings clearly differ from one another in physical characteristics, personality, and other aspects. These *phenotypes* can be either qualitative or quantitative. A *qualitative phenotype* is a trait that can be categorized into two (or more) mutually exclusive groups (e.g., affected or unaffected; unaffected, mildly or severely affected). For example, a person can be classified dichotomously as either having hypertension or not. The underlying *quantitative phenotype* is a continuous measurement of the person's blood pressure. Genetic epidemiology aims to understand the contribution of host genetics to complex diseases and quantitative phenotypes, and to identify their relative importance. A glossary of genetic terms appears at the end of this chapter.

TRADITIONAL GENETICS

Traditional medical genetics has focused primarily on single-gene traits that follow the transmission patterns outlined by Gregor Mendel, a 19th century Austrian

monk. Mendelian diseases are typically rare in the population and can be classified by their transmission as autosomal dominant, autosomal recessive, X-linked dominant, or X-linked recessive. Some Mendelian diseases, for example, cystic fibrosis (the most common autosomal recessive disease in populations of Northern European ancestry, with a birth prevalence of 1/2,500 livebirths among non-Hispanic White populations in the United States) and sickle cell disease (the most common hemoglobinopathy among populations of West African ancestry with a birth prevalence of 1/360 live births in the US Black population are almost always due to mutations in a single gene (respectively, *CFTR* on chromosome 7 and *beta globin* on chromosome 11). Although cystic fibrosis was a lethal disease of childhood for most of human history due to its severe nutritional and pulmonary effects, today patients survive into adulthood with appropriate medical care. There are hundreds of different mutations identified in *CFTR*, but one three-base-pair deletion (Δ508) is by far the most common. Carrier screening followed by appropriate genetic counseling can reduce the burden of this disease in some populations,[1] while newborn screening aids in the early identification and treatment of affected individuals early in life. Sickle cell disease is a debilitating disease with an elevated overall mortality rate but is not uniformly lethal.[2] Universal newborn screening for sickle cell disease in the United States was first introduced in 1975,[3] and now allows early diagnosis, initiation of penicillin prophylaxis, and comprehensive care of affected children, which have significantly reduced childhood mortality from this disease.[4]

Mendelian diseases are not individually common enough to be considered a major public health burden across all populations. However, when all Mendelian diseases are considered together, they do represent a large public health problem, especially for the pediatric health care system. Furthermore, newborn screening programs have been used for over 50 years to identify infants with inborn errors of metabolism (many of which reflect Mendelian diseases), and these programs are now functioning in most developed and many developing countries. While each of the 30 to 60 diseases commonly included in current newborn screening programs in the United States is quite rare, the sensitivity and specificity of screening tests are high enough, and the costs are low enough, to make this a valuable tool for public health.[5] For example, phenylketonuria is characterized by a genetically determined deficiency of phenylalanine hydroxylase, and a child homozygous for this mutation cannot metabolize the essential amino acid phenylalanine. The resulting excess phenylalanine levels lead to severe intellectual disability. While we cannot prevent occurrence of this genotype, through newborn screening we can reduce or eliminate dietary phenylalanine for affected children and therefore prevent severe intellectual disability. Thus, from standpoints of both clinical medicine and public health, newborn screening programs can identify those at risk at the earliest opportunity and maximize the effects of available intervention.

COMPLEX DISEASES

Most human diseases, however, are controlled by some combination of genetic *and* environmental factors acting together. The spectrum of genetic control over diseases varies from strictly genetic to strictly environmental, and some diseases fall in the middle range where both genes and environmental factors influence risk. These include some congenital malformations and cancers, where there is strong and compelling evidence for familial aggregation of risk (the hallmark of genetic control), but also recognized environmental risk factors (e.g., *in utero* exposure to viruses, exposures to carcinogens for cancers, etc.). Unlike the traditional single gene diseases, a complex disease often reflects the effects of one or more genes (that may interact with each other) and the environment, and there is often some degree of etiologic heterogeneity where multiple genes can lead to disease.

Clearly, disease does not necessarily develop in everyone exposed to any particular environmental risk factor. Even if the relative risk of developing the disease is high given exposure to a specific factor, the notion of attributable risk conveys the message that not all occurrences of a disease are due solely to the exposure in question. For example, the relationship between cigarette smoking and lung cancer has been clearly documented. However, lung cancer does not develop in everyone who smokes, and it can develop in nonsmokers. Either another environmental factor is needed in addition to cigarette smoking, or individuals differ in their genetic susceptibility to smoking-induced lung cancer, or both environment and genetics contribute to risk.

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The interaction of genetic and environmental factors was succinctly described many years ago by Lancelot Hogben, who wrote:

> *Our genes cannot make bricks without straw. The individual differences which men and women display are partly due to the fact that they receive different genes from their parents and partly due to the fact that the same genes live in different houses.*[6]

How Epidemiologic Study Designs Can Clarify the Roles of Genetic and Environmental Factors in Risk to Disease

In this chapter, we discuss how some common epidemiologic study designs can be extended to identify genetic factors that contribute to disease causation. Clearly, if genetic factors do influence risk of disease, relatives of cases (individuals with the disease) should be at a higher risk than relatives of controls (individuals without the disease). Therefore, when doing a conventional case-control study it is quite possible to assess familial aggregation by simply asking about the disease status in relatives of both cases and controls. Reliable information can be garnered on first-degree relatives (parents, siblings, and children), and most individuals have some information on second-degree relatives (half-siblings, avuncular relatives, grandparents/grandchildren, etc.). However, beyond close family members it becomes more difficult to obtain reliable information through direct interview of only the index person (i.e., the case or control), and such information is likely subject to information and selection biases.

History from self-reported data on the prevalence of disease in relatives can be summarized as a simple binary variable (i.e., family history positive or negative) or stratified by type of relatives (i.e., number of affected male relatives). Either way, family history information is treated as a risk factor, and a risk ratio (in this case, the odds ratio) can be computed and tested for its statistical significance. If valid information on risk in the population by age, gender, and birth cohort is available for the disease, such as, for example, in population registries (such as population-based cancer registries), this risk ratio can be viewed as a standardized incidence ratio for the entire family. Note, however, that families share more than genes. Common exposures to environmental factors (e.g., passive smoking, diet) may explain, at least partly, the level of familial aggregation.

Twin Studies

Studies of twins have been of great value in identifying the relative contributions of genetic and environmental factors to the causation of human disease. There are two types of twins: monozygotic or MZ (identical) and dizygotic or DZ (fraternal). MZ twins arise from the same fertilized ovum and share 100% of their genetic material. However, DZ twins are genetically like other siblings and thus share, on the average, 50% of their genetic material.

If we look at the occurrence of a disease in MZ twins—who, in effect, have identical genetic material—what are the possible findings? Both twins (twin A and twin B) may have the disease, or both twins may not have the disease; that is, the pair may be *concordant* for the disease. It is also possible that twin A has the disease and twin B does not (or vice versa); that is, the twin pairs are *discordant* for the disease.

If MZ twins are concordant for a disease, what does that tell us about the role of genetic factors? Could the disease be genetic? Yes, because the twins have identical genetic material. Could it be environmental? Yes, because it is well recognized that parents often raise MZ twins similarly, and they obviously shared the same *in utero* exposures, so they are exposed to many of the same gestational environmental factors. However, even if shared exposure to environmental factors were the same for MZ and DZ twins, type of placentation may influence twin concordance. MZ twins' placentas can be either monochorionic or dichorionic, whereas in DZ twins they are always dichorionic. Thus, *in utero* exposure to an environmental factor to the same degree in MZ and DZ twins may result in more concordance in the outcome for the former than for the latter, as placental blood vessel anastomoses in monochorionic placentas that characterize many MZ twins may lead to a greater sharing of the environmental exposure than that in dichorionic placentas. It is interesting that in MZ, but not in DZ twins whose mothers had been equally exposed to thalidomide during pregnancy, concordance for birth defects was almost universal.[7] Thus, observing concordance in MZ twins does not prove a disease is genetic or environmental in origin, but observing discordance in MZ twins does indicate some role for environmental risk factors. Because the discordant MZ twins share the same genetic material, the disease would have to be at least partly environmental in origin.

In DZ twins, both environmental and genetic factors are operating. If a disease is genetic, we would expect lower concordance in DZ twins than in MZ twins, because they share fewer alleles on average. One key assumption of twin studies is that both MZ and DZ twins share environmental factors to the same degree, which may be violated if MZ twins are treated more similarly than DZ twins by their parents and other family members. Other key assumptions are the absence of assortative mating (defined as the tendency for individuals to choose a mate that is either more or less similar to themselves in phenotypical characteristics, as mentioned again later in this chapter) and consanguinity among parents of twins.[8]

How do we calculate the rates of concordance and discordance in twins? Fig. 16.1 shows a cross-tabulation of twins 1 and 2. The numbers in each cell are the numbers of *twin pairs:* thus, there are *a* pairs (in which both twin 1 and 2 have the disease); *d* pairs (in which neither twin 1 nor 2 has the disease); *b* pairs (in which twin 1 does not have the disease but twin 2 does); and *c* pairs (in which twin 1 has the disease but twin 2 does not).

If we want to calculate the concordance rate in twins, most twins will fall into the *d* category; that is, neither will have the disease. We therefore usually look at the other three cells—those twin pairs in which at least one of the twins has the disease. We can calculate the concordance rate in twin pairs in which at least one twin has the disease as follows:

$$\text{Concordance rate} = \frac{a}{a+b+c}$$

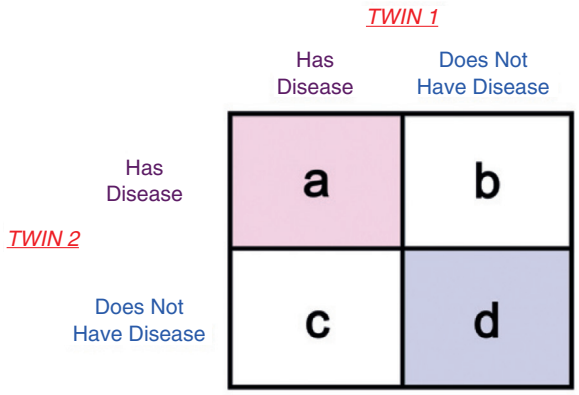

Fig. 16.1 Concordance in twins for a dichotomous variable, such as leukemia.

We can also calculate the discordance rate in all twin pairs in which at least one twin has the disease as:

$$\text{Discordance rate} = \frac{b+c}{a+b+c}$$

Table 16.1 shows concordance data for leukemia in MZ and DZ twin pairs. We see the percentage of concordant pairs is notably high for congenital leukemia, which strongly suggests a major genetic component when the disease occurs near the time of birth. However, the number of twins is small (especially for DZ twins) with perinatal/congenital leukemia and there would be confounding between truly genetic causes and intra-uterine factors, which are shared by all twins.

How are concordance data used? Let us look at a few examples. Table 16.2 shows reported concordance

TABLE 16.1 Age Distribution in Published Clinical Reports of Childhood Leukemia in Twins, 1928–74

	MONOZYGOTIC PAIRS		DIZYGOTIC PAIRS	
	Concordant	Discordant	Concordant	Discordant
Perinatal–congenital	14	1	1	1
Age 2–7 years	6	13	3	5
Age 7–12 years	1	8	–	1
Age 12 years and older	5	14	0	3
Total	**26**	**36**	**4**	**10**

From Keith L, Brown ER, Ames B, et al. Leukemia in twins: antenatal and postnatal factors. *Acta Genet Med Gemellol.* 1976;25:336–341.

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TABLE 16.2 Concordance for Alcoholism in Monozygotic (MZ) and Dizygotic (DZ) Twin Pairs Identified Through an Alcoholic Member

		CONCORDANCE		
Author (Year)	No. of Twin Pairs	MZ (%)	DZ (%)	Ratio of MZ:DZ Concordance
Kaij (1960)	174	71	32	2.2
Hrubec et al. (1981)	15,924	26	13	2.0
Murray et al. (1983)	56	21	25	0.8
Pickens et al. (1991)	86 (M)	59	36	1.6
	44 (F)	25	5	5.0

Modified from Lumeng L, Crabb DW. Genetic aspects and risk factors in alcoholism and alcoholic liver disease. *Gastroenterology*. 1994;107:572–578.

rates for alcoholism in MZ and DZ twins reported by several studies.[9–12] Almost all the reported studies show higher concordance rates for MZ than for DZ twins; the findings from only one study of a relatively small number of twins were not consistent with the findings of the other studies. Thus, these data from the literature strongly suggest a genetic component in the etiology of alcoholism.

It should be pointed out that zygosity is often based on different information across twin studies, and when examining data such as those shown in Tables 16.1 and 16.2, we must ask how twin pairs were labeled MZ or DZ? (Remember the caveat discussed earlier: If you are shown differences between groups or changes over time, the first question to ask is: Are they real? If you are convinced that a difference or change is real and not artifactual, then and only then should you proceed to interpret the findings.) The best way to classify zygosity is by comparing genetic markers between co-twins (which should consistently show 100% identity for MZ twins and 50% for DZ twins); however, DNA may not always be available. Questionnaire data collected from the twins, or their parents are generally accurate enough if questions are included about how often one twin was mistaken for their co-twin by parents, teachers, or other family members, and how physically similar they appeared in childhood. This classification of zygosity is almost as accurate as tests using genetic markers.

So far, we have discussed concordance for a discrete variable, such as leukemia or schizophrenia, which is either present or absent. However, we are often interested in determining concordance for a continuous phenotype, such as blood pressure. In this case, we would plot the data for twin 1 against the data for twin 2 for all twin pairs and calculate the intra-class correlation coefficient *(r)*, which measures the correlation of identical values, as seen in Fig. 16.2. The correlation coefficient ranges from −1 to +1. A correlation coefficient of +1 indicates a full (perfect) positive correlation, 0 indicates no correlation, and −1 indicates a full inverse (opposite) correlation. If we plot such data for MZ twin pairs and for DZ twin pairs, as shown in Fig. 16.3, we expect to find a stronger correlation for MZ twins compared to DZ twins if the quantitative phenotype is under genetic control. Using quantitative phenotypes within a classic twin design offers the opportunity to estimate a purely additive genetic component (due to transmitted alleles at unobserved genes), a residual component (reflecting random factors not shared between co-twins), and either a shared environmental component or a genetic component (that represents

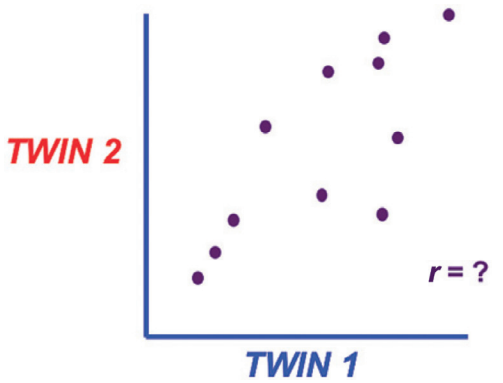

Fig. 16.2 Scatterplots illustrating correlation in twins for a continuous variable, such as systolic blood pressure. This is typically summarized as a correlation coefficient r^2.

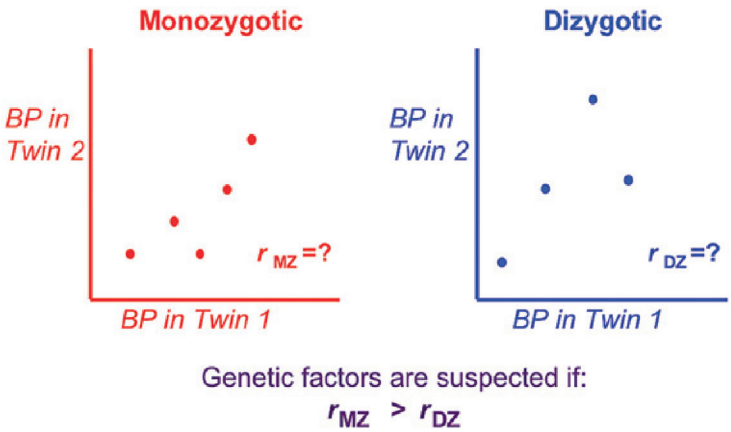

Fig. 16.3 Scatterplots illustrating correlation for continuous variables, such as blood pressure *(BP)*, in monozygotic and dizygotic twins to explore the etiologic role of genetic factors in controlling a continuous variable. Monozygotic twins should have a higher correlation than dizygotic twins.

TABLE 16.3 Correlation Among Relatives for Systolic Blood Pressure

Relatives Compared	Correlation Coefficients
Monozygotic twins	0.55
Dizygotic twins	0.25
Siblings	0.18
Parents and offspring	0.34
Spouses	0.07

Modified from Feinleib M, Garrison MS, Borhani N, et al. Studies of hypertension in twins. In: Paul O, ed. *Epidemiology and Control of Hypertension*. New York: Grune and Stratton; 1975:3–20.

interaction between alleles at a single gene).[8] It is important to realize these latter two components are confounded with one another under the classic twin design where only data on the twins themselves are available. Extending the study to include other family members of the twins creates more contrasts thus allowing further modeling using more elaborate statistical tools.

Table 16.3 shows correlation coefficients for systolic blood pressure among relatives. The highest coefficient is seen in MZ twins; the values for DZ twins and ordinary siblings are close. Also of interest is that virtually no correlation exists between spouses. A strong correlation between spouses (who are generally not biologically related) would suggest a role for environmental factors. However, an alternate suggestion could be that people seek out individuals like themselves for marriage (termed "assortative mating" defined earlier in this chapter). Thus, individuals who are overweight, for example, may seek out other individuals who are also overweight for marriage. In such a situation, we might arrive at a higher spousal correlation for weight or body mass index, and this would happen even for conditions that are not environmentally determined.

A large twin study was reported by Lichtenstein and colleagues in 2000.[13] This study was conducted to estimate the relative contributions of environmental and genetic factors in the causation of cancer. Data from 44,788 twin pairs listed in the Swedish, Danish, and Finnish twin registries were used to assess cancer risks at 28 anatomic sites in twins. Twins of persons with stomach, colorectal, lung, breast, and prostate cancer had an increased risk of developing the same type of cancer. The findings of this and other cancer studies emphasize the need to consider the effects of both genetic and environmental factors (and their interactions) in addressing the etiology of different cancers.

Adoption Studies

We have said that one problem in interpreting the findings from twin studies is that even MZ twins who share the same genetic constitution also share much of their environment. In such studies, it is therefore difficult to tease out the relative contributions of genetic and environmental factors to the cause of disease. One common approach to tease apart this issue is to compare different

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groups of adopted children, their adoptive parents (or family members), and their biologic parents. For example, if we are interested in whether schizophrenia is primarily genetic or environmental in its origin, we can conduct a study using adopted children. There are three basic contrasts:

1. Offspring of non-schizophrenic biologic parents reared by schizophrenic adopting parents
2. Offspring of non-schizophrenic biologic parents reared by non-schizophrenic adopting parents
3. Offspring of schizophrenic biologic parents reared by non-schizophrenic adopting parents

We can examine offspring of non-schizophrenic biologic parents who are adopted and reared by schizophrenic parents. If the disease is purely genetic in origin, what would we expect the risk of schizophrenia to be in these adopted children? It should approximate what is seen in the rest of the population because the family environment would not have any effect in increasing risk. If the disease is largely environmental, we would expect that being reared in an environment with schizophrenic adoptive parents would increase the risk of schizophrenia in these adopted children. As a control group, we could also examine offspring of non-schizophrenic biologic parents reared by non-schizophrenic adoptive parents, and we would expect them to have the population rate of schizophrenia. Obviously for diseases with low prevalence, it will be difficult to find affected adopting parents, so the third option is most frequently used where the children of schizophrenic biologic parents who were adopted by non-schizophrenic parents are assessed for increased risk of disease.

When interpreting data from adoption studies, certain factors need to be kept in mind. The first is the age at which the adoption took place. For example, if the adoption occurred in late childhood, part of the child's environment may have been influenced by their biologic parents. Ideally, we would like to study children who are adopted at birth. Another complicating issue is that, after adoption, some children maintain relationships with their biologic parents, including visits and other exposures to the environment of the biologic parents, so that the separation between the environment of the biologic parents and that of the adoptive parents is not complete.

Many adoption studies have been conducted in Scandinavian countries, which have excellent disease registries including the entire populations, maintain adoption registries, and can link the various population registry systems. As an example, Table 16.4 shows data from a study of schizophrenia carried out by Kety and Ingraham in which they studied rates of schizophrenia in biologic and in adoptive relatives of adopted children.[14] Using data from a nationwide adoption registry and psychiatric hospital records, they identified 34 adoptees who later became schizophrenic, and also identified 34 adoptees without serious mental disease. They then examined the rates of schizophrenia in the biologic and in the adoptive relatives of the schizophrenic adoptees and in control adoptees. The rate of schizophrenia in the biologic relatives of the schizophrenic adoptees was 5.0%, compared with 0.4% in the biologic relatives of adoptees without serious mental disease. The findings strongly suggest a genetic component for the etiology of schizophrenia.

Table 16.5 shows the correlation coefficients for parent-child aggregation of blood pressure, comparing biologic children with adopted children. Clearly, the correlations are much weaker (near 0) for correlations between parents and adopted children than correlations

TABLE 16.4 Schizophrenia in Biologic and Adoptive Relatives of Adoptees Who Became Schizophrenic (National Study of Adoptees in Denmark)

	BIOLOGIC RELATIVES			ADOPTIVE RELATIVES		
		SCHIZOPHRENIC			SCHIZOPHRENIC	
	Total No.	No.	%	Total No.	No.	%
Adoptees who became schizophrenic ($N = 34$)	275	14	5.0	111	0	0
Control adoptees (no serious mental disease) ($N = 34$)	253	1	0.4	124	0	0

From Kety SS, Ingraham LJ. Genetic transmission and improved diagnosis of schizophrenia from pedigrees of adoptees. *J Psychiatr Res.* 1992;26:247–255.

TABLE 16.5 Correlation Coefficients for Parent-Child Aggregation of Blood Pressure

	BETWEEN PARENTS AND	
	Biologic Child	Adopted Child
Systolic	0.32 ($P < .001$)	0.09 (NS)
Diastolic	0.37 ($P < .001$)	0.10 (NS)

NS, Not significant.
Modified from Biron P, Mongeau JG, Bertrand D. Familial aggregation of blood pressure in 558 adopted children. *Can Med Assoc J.* 1976;115:773–774.

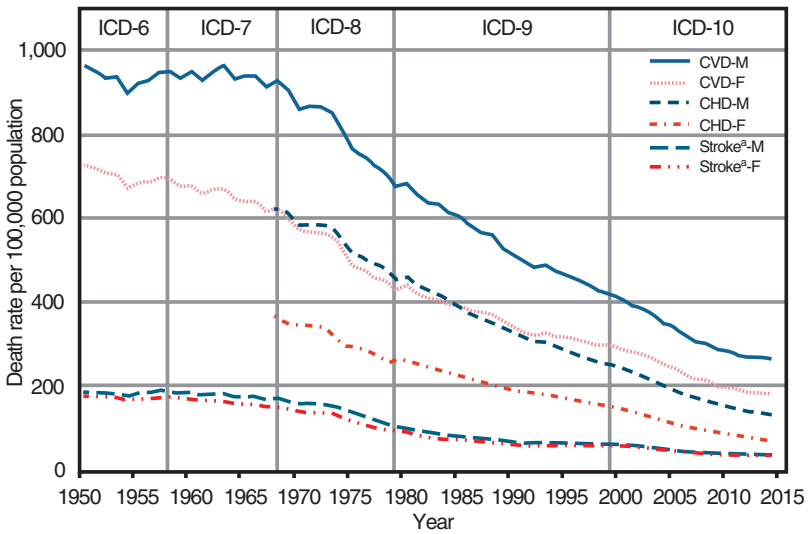
between parents and biologic children. The findings strongly suggest a genetic component for blood pressure, a quantitative trait.

TIME TRENDS IN DISEASE INCIDENCE

If we observe time trends in disease risk, with incidence either increasing or decreasing over a relatively short period of time, and if we are convinced that the trend is real, the observation implicates environmental factors in the causation of the disease. Clearly, genetic characteristics of human populations generally do not change over relatively short time periods. Thus, the change in mortality from coronary heart disease (CHD) in men from 1979 to 2004 seen in Fig. 16.4 may be primarily due to changes in exposure to environmental factors. (Mortality may have also decreased because of improvements in medical care of patients with CHD.)

Fig. 16.5 shows age-adjusted death rates for stomach cancer in men in several countries. The highest rate is seen in Japan, and the rates in the United States are quite low. Are these differences real? Could they be due to differences in quality of medical care or in access to medical care in different countries? Could they be due to international differences in how death certificates are completed? Results of other studies suggest that these differences are real and likely due to differences in the prevalence of an environmental factor known to be a probable necessary cause of stomach cancer, *Helicobacter pylori* infection. (Furthermore, as case fatality for stomach cancer is high, these between-country differences probably reflect differences in the incidence of this cancer.)

Fig. 16.6 shows comparable data for breast cancer in women. Here we see that one of the lowest rates in the world is in Japan. Are differences between countries due to environmental or genetic factors? Again,



[a]The comparability ratio 1.0502 was applied to the death rates reported in vital statistics for 1979–1998. Source: CDC/NCHS, National Vital statistic System, Morality Multiple-Cause-of-Death. These data represent underlying cause of death only.

Fig. 16.4 Age-adjusted cardiovascular disease *(CVD)* mortality rates by sex, 1950–2014. *CHD,* Coronary heart disease; *F,* female; *ICD,* International Classification of Diseases; *M,* male. (From Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. *Circ Res.* 2017;120:366–380.)

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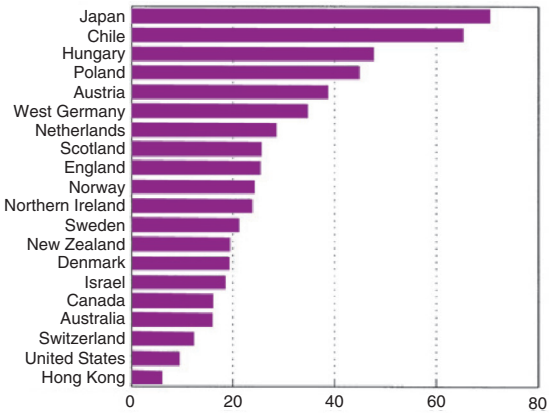

Fig. 16.5 Age-adjusted death rates per 100,000 for stomach cancer in 20 countries, men, 1976–77. (Data from Page HS, Asire AJ. *Cancer Rates and Risks*. 3rd ed. Washington, DC: US Government Printing Office; 1985, NIH Publication No. 85–691.)

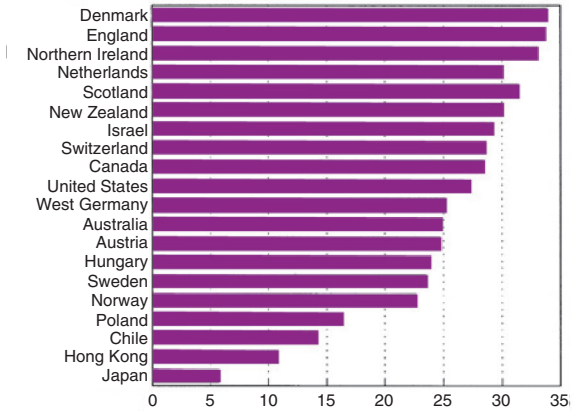

Fig. 16.6 Age-adjusted death rates per 100,000 for breast cancer in 20 countries, women, 1976–77. (Data from Page HS, Asire AJ. *Cancer Rates and Risks*. 3rd ed. Washington, DC: US Government Printing Office; 1985, NIH Publication No. 85–691.)

environmental influences are probably more important in the etiology of breast cancer, even though some genes are known to cause this disease (e.g., *BRCA1* and *BRCA2*), but these recognized genes cannot explain most of the variation in risk.[15,16]

How can we tease apart the relative contributions of genetic and environmental factors to international differences in risk of disease? We can do so by studying migrants in a manner analogous to that just described for studying adoptees.

TABLE 16.6 Standardized Mortality Ratios for Cancer of the Stomach in Japanese Men, Issei, Nisei, and US White Men

Group	Standardized Mortality Ratio
Japanese men	100
Issei[a]	72
Nisei[a]	38
US White men	17

[a]Issei and Nisei are first- and second-generation Japanese migrants, respectively.
From Haenszel W, Kurihara M. Studies of Japanese migrants: I. Mortality from cancer and other disease among Japanese in the United States. *J Natl Cancer Inst*. 1968;40:43–68.

Migrant Studies

Let us assume that a Japanese individual living in Japan—a country with a high risk for stomach cancer—moves to the United States, a country with a low risk of stomach cancer. What would we expect to happen to this person's risk of stomach cancer? If the disease is primarily genetic in origin, we would expect the high risk of stomach cancer to be retained even when people move from a high-risk to a low-risk area. However, if the disease is primarily environmental in origin, we would expect that over time the risk for such a migrant group would shift toward the lower risk of the adoptive country.

Table 16.6 shows standardized mortality ratios (SMRs) for stomach cancer in Japanese men living in Japan, Japanese men who migrated to the United States ("Issei"), and the children of the Japanese migrants ("Nisei") born in the United States, compared with SMRs of US White males. We see the SMRs progressively shift toward the lower SMR of US White males. These data strongly suggest that a significant environmental component is involved. For example, as mentioned previously, it is well known that the prevalence of an important cause of stomach cancer, *Helicobacter pylori* infection, varies among countries.[17]

However, we should bear in mind that when people migrate to another country, they and their families do not immediately shed the environment of their homeland. Many aspects of their original culture are retained, including certain dietary preferences. Thus, the microenvironment of the migrant, particularly environmental characteristics related to lifestyle, are generally a

combination of their country of origin and those of the country of adoption. Another important consideration is the age at which the person migrated; in interpreting the findings from migrant studies, it is important to know how much of the person's life was spent in each country.

Let us turn to another example. The risk of multiple sclerosis has been shown to be related to geographic latitude: the greater the distance from the equator, the greater the risk.[18] This observation is very intriguing and has stimulated much research. However, questions remain about the extent to which the relationship of MS to latitude is a result of environmental factors, as well as about how we can determine which environmental factors might be involved.

Studies of people who have migrated from high-risk to low-risk areas are ideally suited to addressing some of these questions. One country that lent itself nicely to such a study is Israel, which, by latitude, is a low-risk country for multiple sclerosis. Israel had successive waves of immigration during the 20th century. Some of the migrants came from high-risk areas, such as the relatively north latitudes of the United States, Canada, and Northern Europe, whereas others came from low-risk latitudes closer to the equator, including areas of North Africa and the Arabian Peninsula.

Table 16.7 shows data for the incidence of multiple sclerosis in European and African and Asian migrants into Israel. This disease is not common; therefore, the sample is small (only 67 cases among 668,880 migrants). Let us look at the rates for African and Asian migrants who moved from one low-risk area to another.

TABLE 16.7 Incidence of Multiple Sclerosis (MS) per 100,000 Among European, African, and Asian Immigrants to Israel by Age at Immigration

	INCIDENCE OF MS IN MIGRANTS	
Age at Immigration	European	African and Asian
<15 years	0.76	0.65
15–29 years	3.54	0.40
30–34 years	1.35	0.26

Modified from Alter M, Leibowitz U, Speer J. Risk of multiple sclerosis related to age at immigration to Israel. *Arch Neurol.* 1966;15:234–237.

Their risk remained low. Now examine the data for European migrants who migrated from a high-risk area (Europe) to a low-risk area (Israel). Europeans who migrated before the age of 15 years (top row) had a low rate, like that of African and Asian migrants. However, Europeans who migrated after the age of 15 years tended to retain the high rate of their country of origin. These findings suggested risk of multiple sclerosis is determined in childhood and the critical factor is whether childhood years were spent in a high-risk or a low-risk area. A person who spent childhood years in a low-risk area remains at low risk; one who spent childhood years in a high-risk area remains at high risk, even after later migration to a low-risk area. This suggests some event in childhood may be of importance in causing multiple sclerosis.

What are the problems with migrant studies? First, migrants are not representative of the populations of their countries of origin. Therefore, we must ask what selection factors led certain people to migrate? For example, people who are seriously ill or disabled generally do not migrate. Other factors, including socioeconomic and cultural characteristics, are also related to which persons are likely to migrate and which persons are not. Consequently, given this problem of selection, we must ask whether we can legitimately compare the rates of stomach cancer among Issei and Nisei with the rates in native Japanese. Second, we need to ask what the age at migration was. How many years did the migrants spend in their country of origin and how many in their adopted country? Third, we should remember migrants do not completely shed the environment of their country of origin after they migrate. These and other factors need to be considered in interpreting the results of migrant studies. There is an obvious parallel with adoption studies, and as seen in Table 16.8, many of the issues that arise in interpreting the findings are similar for the two types of studies.

HOW GENETIC MARKERS ARE USED TO MAP GENES CONTROLLING RISK TO DISEASES, INCLUDING COMPLEX DISEASES

Genetic markers are variants in DNA sequence that can be typed directly. Markers are transmitted from parent to offspring, clearly following regular Mendelian

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TABLE 16.8 Issues in Interpreting the Results of Adoption and Migrant Studies

Adoption Studies	Migrant Studies
• Adoptees are highly selected.	• Migrants are highly selected.
• Age at adoption varies.	• Age at migration varies.
• Adoptees may retain various degrees of contact with their biologic parent(s).	• Migrants may retain many elements of their original environment, particularly those related to culture and lifestyle.

patterns, and the chromosomal locations of genetic markers are largely known. If the marker is polymorphic in the population, then many people will carry one or another allele at the marker, and there will be reasonable numbers of heterozygotes and both homozygotes for biallelic markers. While blood groups (like the ABO blood type) qualify as a genetic marker, the most common form of genetic markers are single nucleotide polymorphisms (SNPs). Most SNPs do not have any direct physiologic effects, but a minority occur in coding or regulatory regions of a gene and may directly affect an individual's susceptibility to disease or response to medical treatments.

The ultimate purpose of mapping studies is to identify genes associated with susceptibility to a disease to enhance our understanding of disease pathogenesis and to facilitate development of appropriate preventive strategies. The search for disease susceptibility genes uses two main approaches:

1. Use of family studies to identify *linkage* or co-segregation between a certain marker and a possible disease gene.[19] The coinheritance of genetic markers and disease represents compelling evidence that such a gene does exist while localizing the potentially causal gene to a specific chromosomal region. However, if there are multiple genes that can cause the same disease, they would show evidence of *linkage heterogeneity*, where some families provide evidence of linkage to a given marker while others do not.
2. Search for an *association* between a marker allele and a disease using samples of unrelated people. While even strong evidence of association remains somewhat less compelling evidence of direct causality, and such evidence is subject to possible confounding due to heterogeneity within the sample, the methods for testing the statistical association between disease and genetic markers build upon conventional epidemiologic study designs and are relatively easy to implement.

Linkage Analysis in Family Studies

As mentioned earlier, when a person has a certain disease, it is valuable to examine their first-degree relatives for evidence of a greater-than-expected prevalence of disease. Excess risk in first-degree relatives suggests (though does not prove) the existence of some genetic component. It is also possible to examine high-risk families, such as the pedigree shown in Fig. 16.7, which shows a multiplex family with retinoblastoma across

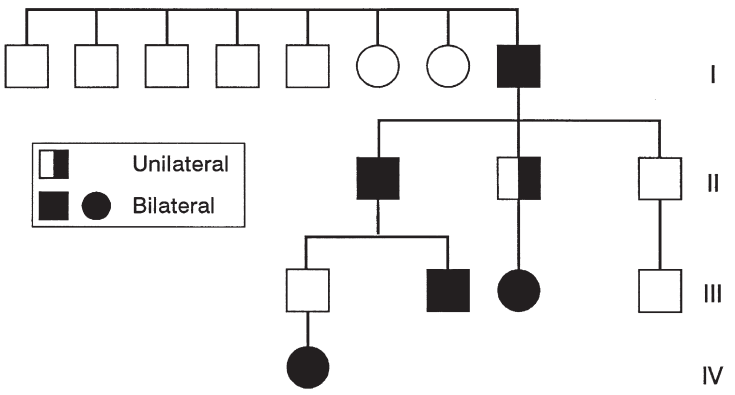

Fig. 16.7 Pedigree of family reported with retinoblastoma occurring in four successive generations. *Squares*, men; *circles*, women. (From Migdal C. Retinoblastoma occurring in four successive generations. *Br J Ophthalmol.* 1976;60:151–152.)

four successive generations. Such pedigrees not only give a visual picture of the familial nature of this disease but can also be used to map the disease gene by testing for *co-segregation* with one genetic marker (or many markers, as in a genome-wide scan). Clearly this family is likely to reflect an autosomal dominant gene controlling risk. Note how this pedigree also demonstrates how even in high-risk families, the disease may skip generations and be transmitted by individuals *(male in the third generation who has a female offspring with disease)* who are not affected themselves (generally denoted as "incomplete penetrance" of the putative disease gene).

Assuming the disease gene has a rare, autosomal dominant mutation that causes retinoblastoma, linkage can be tested between a genetic marker and the hypothetical disease gene. *Linkage analyses* seek to determine whether alleles from two loci (the hypothetical disease locus and some genetic marker) segregate together in a family and are passed as a unit from parent to child. Genes physically near each other on the same chromosome (i.e., the two linked genes) will tend to be transmitted together; that is, they will co-segregate. Genetic linkage can only be identified through family studies, and generally requires multi-generational families with many affected individuals (termed multiplex families). Some information about linkage can be obtained from nuclear families (two parents and several full siblings) if two or more of the offspring are affected. However, even when linkage is demonstrated in some families, it may not show any evidence of linkage in other families if two different genes control risk; that is, if there is linkage heterogeneity. Furthermore, the cases of disease in multiplex families needed for linkage analysis are not fully representative of all cases of disease. Linkage often sheds light on the biologic mechanisms underlying the transmission and pathogenesis of disease. For example, the causal gene for polycystic kidney disorder, an autosomal dominant disease, has been characterized. As seen in the family shown in Fig. 16.8, the 1-allele shows evidence of linkage with disease and is seen in the father and two of his offspring, all of whom were affected. In the case of cystic fibrosis (Fig. 16.9), an autosomal recessive condition, the causal variant must be inherited from both the father and the mother. Thus, the disease is not seen in either parent, but only in the child who has both alleles.

Association Studies

Like the approach of testing for familial aggregation of disease, we can also test for an association between a

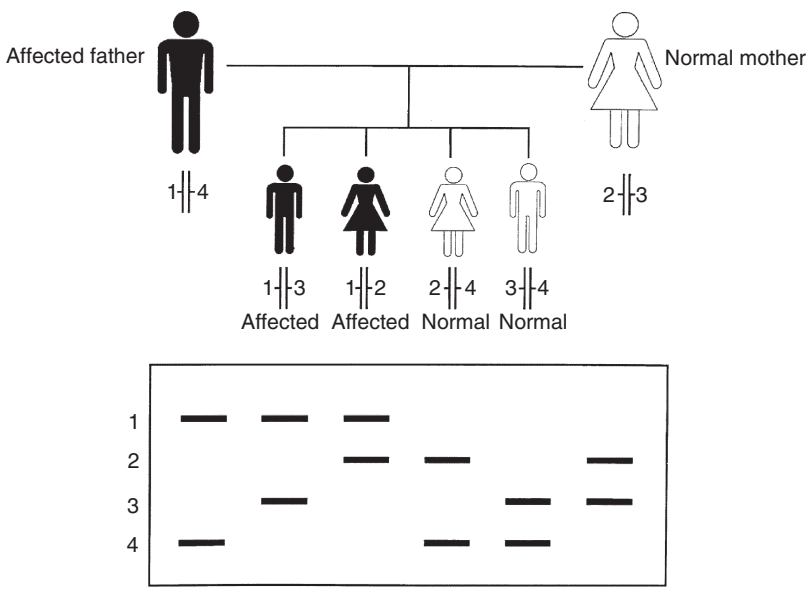

Fig. 16.8 DNA analysis of autosomal dominant disorders. Example: Polycystic kidney disorder. (From Taylor HA, Schroer RJ, Phelan MC, et al. *Counseling Aids for Geneticists*. 2nd ed. Greenwood, SC: Greenwood Genetic Center; 1989.)

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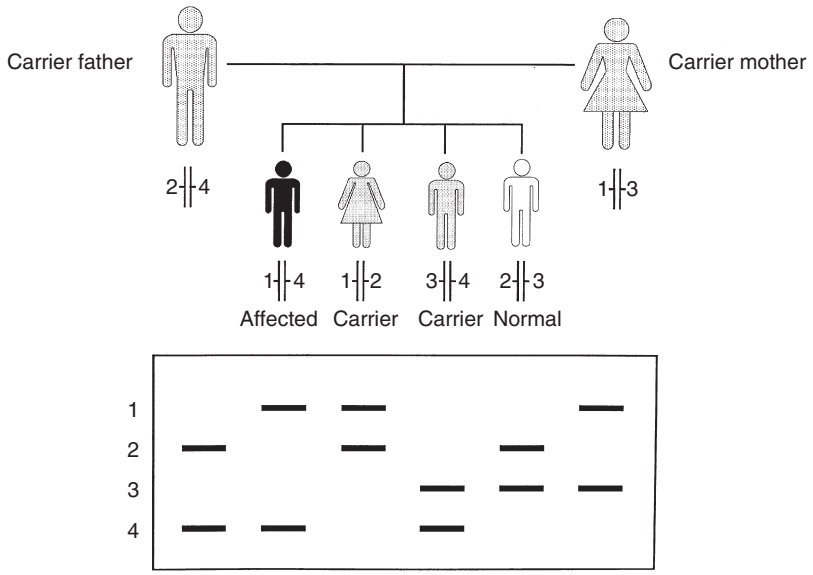

Fig. 16.9 DNA analysis of autosomal recessive disorders. Example: Cystic fibrosis. (From Taylor HA, Schroer RJ, Phelan MC, et al. *Counseling Aids for Geneticists*. 2nd ed. Greenwood, SC: Greenwood Genetic Center; 1989.)

SNP and a disease (or a continuous phenotype). This test of association is the same as that used in traditional epidemiology, but the genetic marker allele or genotype becomes the exposure of interest. We can test for association with a single gene, or a set of genes known to be potentially associated (candidate genes) or agnostically across the entire genome (genome-wide). The feasibility of studying the entire genome to identify genetic associations, in the form of genome-wide association studies (GWAS), has changed the overall approach for studying associations between genetic markers (most often SNPs) and disease. In the GWAS approach, using 1 to 5 million SNPs, we are looking for regions of the genome strongly associated with a disease (and therefore likely to harbor a causal gene), but the individual SNPs yielding evidence of association are generally not directly causal and most often they are in noncoding regions of the genome. However, these significant SNPs may be correlated with some unobserved high-risk allele at an unknown causal gene and can still be useful in mapping nearby genes that do control risk. GWAS have become possible in the last 10 years or so, largely due to technological advances in SNP genotyping; they have been widely used for a variety of common diseases where multiple genes and some environmental risk factors are known to play some role in causing disease.[20,21] The premise underlying GWAS is that common SNPs scattered throughout the genome can "tag" haplotypes (a genetic grouping of genomic variants that tend to be inherited together) with sufficient accuracy to reveal correlations between observed SNPs and unobserved causal genes when analyzed under the traditional case-control or cohort study design. The test statistic (usually a chi-squared test or a logistic regression model, topics not covered in this text) is simple, and significant genotype or allele frequency differences between groups of cases and controls should reveal meaningful differences reflecting either a direct or indirect association between a marker and some unknown causal gene. Because the number of SNPs used in GWAS is large (originally at least 100,000 SNPs but now typically 1 to 2.5 million SNPs per person in a study), the conventional critical value of the alpha error of 5% for each SNP is no longer appropriate because so many tests are being done in each study. To minimize the rate of false-positive results, a genome-wide significance level is set at $P = 5^{*}10^{-7} - 5^{*}10^{-8}$. Since the first GWAS-based discovery of the association of complement factor H (CFH) gene and age-related macular degeneration,[22] more than 2,000 robust associations between genes and

complex diseases have been identified.[23] By combining multiple studies, it is now clear that multiple genes influence the risk of most complex diseases representing major public health burdens.[20] These replicated genetic risk factors should be useful in improving risk prediction (on a broad level), diagnostic classification, and eventually drug development (both for potential efficacy and to minimize adverse events). This progress has generated excitement about precision medicine where genetic information can guide clinical medicine (see later). Recently, Khoury and Evans[24] advocated for a similar emphasis on developing "precision prevention," characterized by strategies building up the role and importance of genetics in public health. The gene-environment interaction, to be further discussed later in this chapter, is also related to precision prevention, as genetic susceptibility to environmental risk factors may markedly increase risk of disease. For example, the interaction of smoking and certain polymorphisms seems to be related to a high risk of sarcoidosis, an autoimmune disease.[25]

Building from association studies, often genome-wide, polygenic scores combine the smaller effects of individual variants to estimate an overall genetic risk for a trait of interest. An individual's score is then compared to a population distribution to determine their relative risk for that outcome.[26] There are several methods to calculate a polygenic score that take effect sizes for individual weights and account for the correlation between them due to linkage disequilibrium through reducing the set of variants and/or down-weighting the effect sizes.[27] After variants are selected and their weights adjusted, the number of risk alleles per individual is multiplied by the effect weights to create an individual score. This score is then compared against a population distribution to determine the individual's relative risk compared to others in the distribution.[28,29]

Polygenic scores (PGS) have multiple potential uses both in population research and precision health. For population-level research, PGS can be used to provide insights in the role of genetic factors versus environmental in the development of a particular outcome,[30] improve efficiency of clinical trials,[31] or as instrumental variables for causal inference based on observational data.[32] Their use at an individual level often center on potential clinical utility to inform patient care. While PGS can be informative on their own, they are often combined with modifiable risk factors to estimate future relative or absolute risk.[33,34] For example, Kachuri et al.[34] quantified the additional predictive value of PGS when combined with family history and relevant modifiable risk factors for 16 cancers. They demonstrated that while the magnitude of improvement differs between cancers and models, the addition of PGS resulted in significant improvement classifying who would develop cancer versus not, compared to family history and non-genetic factors alone.

Many of the problems in methodology and interpretation of results addressed in earlier chapters apply to the associations between diseases and genetic markers. This includes biases (selection, information) and confounding. Selecting appropriate controls is always important. When presented with a list of associations with a disease and a genetic marker (blood group or SNP), we should ask how were the conclusions regarding such associations arrived at, and what comparison groups were used? Thus, the methodologic issues discussed in earlier chapters in the context of different types of epidemiologic study designs are highly relevant when investigating ways in which genetic factors relate to these diseases.

RACE AND ANCESTRY IN GENETIC ASSOCIATION STUDIES

Race and ancestry are two important concepts that can have large direct or indirect impacts in genetic association studies.

The concepts of race, ethnicity, and genetic ancestry can be erroneously conflated within epidemiology, medicine, and public health.[35] This conflation can go both ways, as follows. Often individuals are analyzed in genetic studies by groups defined using racial or ethnic language, such as Hispanic/Latino, when they are meant to be capturing genetic ancestry.[36,37] Conversely, researchers may ascribe differences between racial/ethnic groups to genetic differences without evidence.[35] Unless genetic variants are directly measured and assessed for association with the outcome of interest, conclusions cannot be made regarding the role of genetic risk factors which can reinforce misconceptions about biology and race.[38] It is important to be clear and specific when utilizing these concepts in defining populations, relying on underlying assumptions, and interpreting results.

One important confounder for genetic association studies is ancestry. We know that, despite the genetic

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similarities between individuals (>99%), there are allele frequency differences between people originating from different parts of the world due to the natural variation among human sub-populations, or to possibly selective or environmental pressures present through the history of different sub-populations. Thus, ancestry can be associated both with exposure (allele or genotype frequency) and with the disease outcome, and thus confound the study results. There are methods to address this important confounder, which may include simple stratification by self-reported ancestry or estimating the percentage of each person's ancestry based on genetic markers, including that in the statistical model.

Genetic studies, GWAS in particular, have a well-documented bias with an overrepresentation of European ancestry populations[39,40] which is carried over into clinical scores like polygenic risk scores leading to decreased score performance in non-European ancestry groups.[41,42] Additionally, selection or participation bias in the training dataset can limit the applicability of developed PGS to other populations, especially if these relationships include relevant confounders with the environment and how it can interact with genetics.[43,44] There are also concerns about best practices for the integration of PGS with other standard measures of risk, including monogenic variation, family history, and modifiable risk factors.[45] This is an active area of research as the field charts the best path forward for reproducible and broad applicability of PGS across traits and populations.

INTERACTION BETWEEN GENETIC AND ENVIRONMENTAL RISK FACTORS

The question of genetic susceptibility to environmental factors and the possibility of interaction between them must also be addressed. In Chapter 14, we discussed the study by Grant and Dawson that describes an association of earlier age at onset of alcohol consumption to prevalence of lifetime alcohol abuse (Fig. 16.10). As seen in Fig. 16.11, when the subjects were divided into those with a positive family history of alcoholism and those with a negative family history, the overall relationship still held, although the prevalence was higher among those with a positive family history.[46] This observation suggests that, although the observed relationship between lifetime risk of alcohol abuse and age at initiating alcohol consumption may reflect environmental influences, the effect of family history suggests either an interaction with genetic factors or some influence of child rearing related to a family history of alcohol abuse.

One example of potential gene-environment interaction involves smoking and the factor V Leiden mutation. Smoking is a known risk factor for myocardial

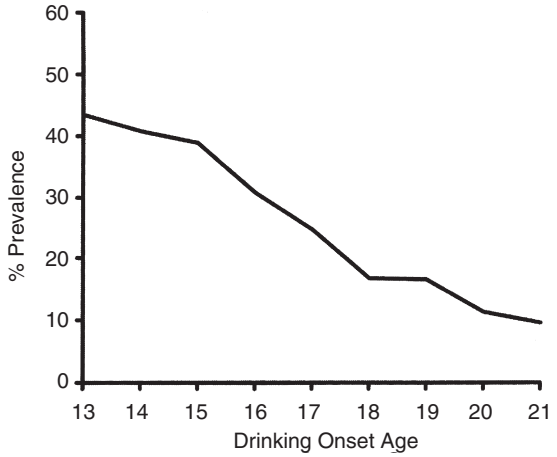

Fig. 16.10 Prevalence of lifetime alcohol dependence by age at drinking onset. (Modified from Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Substance Abuse*. 1997;9:103–110.)

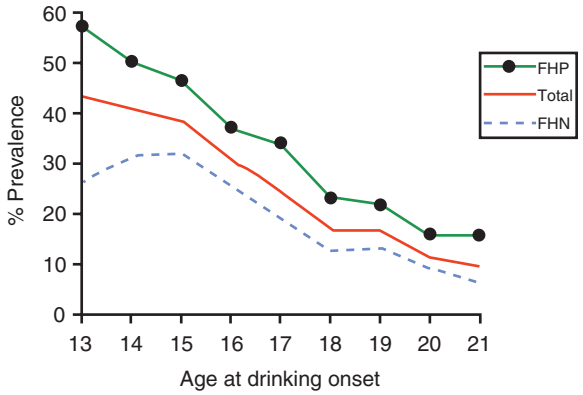

Fig. 16.11 Prevalence of lifetime alcohol dependence by age at drinking onset and family history of alcoholism. *FHN*, Family history negative; *FHP*, family history positive. (Modified from Grant BF. The impact of a family history of alcoholism on the relationship between age at onset of alcohol use and DSM-IV alcohol dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Alcohol Health Res World*. 1998;22:144–147.)

infarction (MI), and factor V Leiden is a common hereditary abnormality that affects blood clotting and increases the risk of venous thrombosis. Rosendaal and colleagues conducted a population-based case-control study of 472 young women, including 84 who had an MI before the age of 45.[47] The factor V Leiden mutation was more prevalent in the MI case group, with an odds ratio of 2.4 as compared to those without this mutation. However, when considering both smoking and carrier status, there is a suggestion of statistical interaction between smoking and the factor V Leiden, as illustrated in Table 16.9. Noncarrier women who smoked showed an odds ratio 9 times more likely to have a premature MI, but carrier women who smoked were 32 times more likely to have a premature MI compared to those women who did not smoke and were not carriers. Because the estimated combined effects of the genotype and smoking greatly exceeded what would be expected under either a multiplicative or an additive model, these findings suggest statistical interaction (or deviation from a simple combination of the independent effects of genotype and environmental exposures). While this type of analysis is intriguing, it is often impossible to say definitively whether such statistical interaction represents true biologic interactions (e.g., synergistic or antagonistic relationships between the effects of genetic and environmental risk factors).[48]

TABLE 16.9 Association of Smoking and Factor V Leiden on Risk of Myocardial Infarction in Young Women

Odds Ratio (95% CI)	FACTOR V GENOTYPE	
Current Smoker	**Wildtype**	**Leiden**
No	1.0 (ref)	1.1 (0.1, 8.5)
Yes	9.0 (5.1, 15.7)	32.0 (7.7, 133)

The risk of myocardial infarction is elevated in young women who smoke but is greatest in those with the factor V Leiden genotype. This statistical interaction between genotype and environment exceeds what would be expected by genetics or environment alone (OR = 32).
CI, Confidence Interval.
From Austin MA, Schwartz SM. Cardiovascular disease. In: Costa LG, Eaton DL, eds. *Gene-Environment Interactions: Fundamentals of Ecogenetics*. Hoboken, NJ: John Wiley & Sons; 2006. Modified from Rosendaal FR, Siscovick DS, Schwartz SM, et al. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. *Blood*. 1997; 89:2817–2821.

There is biologic plausibility, however, for each of these exposures, and their interaction is also biologically plausible. Detecting gene-environment interaction always requires larger sample sizes, and confirming its existence across populations may prove difficult because the allele frequencies and exposure rates can differ across populations, as discussed by Aschard.[49]

In 1995, Brennan and colleagues reported a study of cigarette smoking and squamous cell cancer of the head and neck.[50] They found that in patients with invasive cancer of the head and neck, smoking was associated with a marked increase in mutations in the p53 gene, which is normally a tumor suppressor. Such mutations are likely to contribute to both the inception and the growth of cancers. The investigators studied tumor samples from 127 patients with head and neck cancer and found p53 mutations in 42% (54 of 127) of patients. Patients who smoked at least one pack per day for at least 20 years were more than twice as likely to have mutations in p53 as patients who were nonsmokers. Patients who smoked and drank more than 1 oz of distilled spirits (alcohol) per day were 3.5 times more likely to have mutations in p53 than patients who neither smoked nor drank. As seen in Fig. 16.12, p53 mutations were found in 58% of patients who both smoked and drank; in 33% of patients who smoked but did not drink; and in 17% of patients who neither smoked nor drank. Furthermore, the type of mutation found in patients who neither smoked nor drank seemed likely to be endogenous rather than caused by environmental mutagens (i.e., exogenous). The findings suggest that cigarette smoking may tend to inactivate the p53 tumor

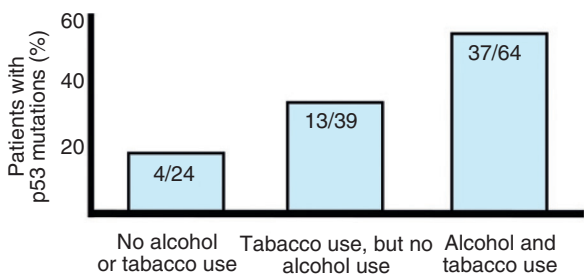

Fig. 16.12 Association of p53 gene mutations with cigarette smoking and alcohol consumption in 129 patients with squamous cell carcinoma of the head and neck. (From Brennan JA, Boyle JO, Koch WM, et al. Association between cigarette smoking and mutation of the p53 gene in squamous cell carcinoma of the head and neck. *N Engl J Med*. 1995;332:712–717.)

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suppressor gene and thus provide a molecular basis for the well-recognized relationship of cigarette smoking to head and neck cancer.

A further step in this approach is to identify a specific gene defect that is associated with a certain environmental exposure. An example is seen in findings linking a specific defect in the p53 gene to aflatoxin exposure in patients with hepatocellular carcinoma (HCC). In Chapter 14, the positive synergism of hepatitis B virus (HBV) and aflatoxin B_1 exposure in increasing the risk of HCC is discussed. To determine whether the frequency of a specific mutation in the p53 tumor suppressor gene (a "hot spot" mutation at codon 249) was related to the risk related to aflatoxin exposure, Bressac and coworkers screened HCC samples from 14 countries.[51] The mutation was found in 17% (12/72) of tumor samples from four countries in southern Africa and the southeast coast of Asia but in none of 95 samples from other geographic locations including North America, Europe, the Middle East, and Japan. The four countries in which the mutation was found, China, Vietnam, South Africa, and Mozambique, have the highest incidence of HCC in the world and share a similar warm and humid climate, which favors the growth of aflatoxin-producing molds. The rate of HBV carriage was high but did not vary significantly among the countries studied. However, the risk of aflatoxin exposure did vary among these countries, and the presence of the mutation was found to correlate with the risk of exposure to aflatoxins.

Further support for these findings was provided by Aguilar and colleagues, who studied samples of normal livers from three geographic areas that varied in their prevalence of aflatoxin exposure: negligible levels (United States), low levels (Thailand), and high levels (Qidong, China).[52] The frequency of the mutation paralleled the level of aflatoxin B_1 exposure, suggesting that aflatoxin has a causal and probably early role in the development of liver tumors.

Thus, studies combining epidemiologic and molecular methods may prove invaluable in confirming an etiologic role for certain environmental agents by demonstrating their specific gene effects. Moreover, such studies may also suggest biologic pathways and mechanisms that may be involved in the development of certain cancers and other diseases. However, combined epidemiologic and molecular studies may also help determine that a disease is not primarily caused by environmental factors. For example, Harris pointed out that the exact nature of the p53 mutation can be valuable in indicating that a certain cancer did not result from an environmental carcinogen but instead was caused by endogenous mutagenesis, such as was seen in the study just described, of patients with head and neck cancer who were nondrinkers and nonsmokers.[53] Germ line mutations in p53 can also indicate that a person has an increased susceptibility to cancer as originally proposed by Knudson in 1971.[54]

However, it must be remembered that statistical power to detect gene-environment effects will generally require much greater sample sizes compared to what is required to detect marginal effects of either the genetic or the environmental risk factor.[49] The rule of thumb is that a fourfold increase in sample size is needed to detect interactions, and sometimes even simple forms of interaction can be difficult to confirm in actual data sets. This is especially true when there is substantial error in measuring the environmental risk factor. Still, if evidence of gene-environment interaction can be obtained, it would open new opportunities for public health intervention, because modifying environmental risk factors is far easier than altering the genetic structure of a population.

PRECISION MEDICINE

Sequencing technology is now driving the current era of genetic epidemiology. Sequencing has the advantage of identifying *all* variants in each region of the genome (i.e., rare and low frequency single nucleotide variants, as well as common tagging SNPs). This new phase has been driven by two forces: (1) the advancements in massive parallel or "next-generation sequencing" technology that is becoming affordable even for samples sizes seen in epidemiologic studies and (2) the impending completion of combined GWAS analyses for many (if not most) complex diseases across large studies, which has identified numerous genes as significantly influencing risk. We have not reached our goal of fully understanding complex diseases (and we might be far from it) if causal pathways involve mechanistic gene-gene and gene-environment interactions. We have gone from originally identifying the double helix in the middle of the 20th century to the ability to sequence the entire genome of many individuals in the first quarter of the 21st century.

Whole genome sequencing is particularly exciting because of its promise of deepening our understanding of genes and for its potential for facilitating the development of "personalized treatments" of individual patients. We previously discussed some limitations of randomized trials in developing new treatment modalities, particularly because the trials generally deal with groups rather than with individuals, and thus usually estimate average effects. Therefore, as pointed out earlier, the study results are often given for groups and leave the treating physician without information regarding how likely it is that a given individual whom he or she is treating will benefit from the new drug, or whether the patient will develop serious side effects from it. However, with the advent of the current new era in human genetics the hope has been that we will be able to develop therapies that are tailor-made for the individual patient based on the characteristics of their genome. For example, the drug clopidogrel is used after the placement of a coronary stent following a heart attack. Clopidogrel depresses platelet activity, which reduces your risk of a heart attack. Loss of function of genetic variants in the CYP2C19 gene result in decreased metabolite production and is associated with the increased risk of a subsequent heart attack,[55,56] even when patients are treated with clopidogrel. However, adjustment of the dose of clopidogrel in patients who have these CYP2C19 alleles (found in nearly one-third of the general US population) or changing the medication to another drug decreases the risk of subsequent heart attacks to the level of patients without these alleles.[57–59] Thus, genetic information generated from populations can be used to treat the individual patient.

PROSPECTS FOR THE FUTURE

Despite the excitement accompanying sequencing of the human genome and the results of genome-wide studies described earlier, for most complex diseases (in which both genetic and environmental factors have been implicated) the current data are still not yet sufficient to specifically delineate how genes control risk. Enhanced understanding of the molecular changes in cancer resulting from studies of genetic changes in cancer cells should improve our understanding of how individuals can vary in their susceptibility to cancers and facilitate the development of specific therapies for biologic pathways involved in different tumors. Such "targeted" or "individualized" therapies may help in understanding and treating subgroups of tissue-specific tumors. By targeting specific molecular pathways involved in different tumors, as well as the points at which tumor cells may be particularly vulnerable to certain therapies, individualized treatment should become more effective. Such treatment might also have fewer and less severe side effects than conventional therapies, which are not specific in their cytotoxic effects and affect both abnormal and normal cells. An example is the use of tamoxifen for estrogen receptor-positive breast cancer.[60]

Childs articulated a concept encompassing not only the different characteristics of histologically different tumors, but also the unique genetic and environmental characteristics of humans that may have led to a vulnerability to such tumors.[61] As a result, what might appear at first glance to be the same disease occurring in different individuals should perhaps be considered different diseases with the same phenotype because the disease in a person is a "package" of physical, laboratory, and other abnormalities, combined with a unique set of genetically and environmentally determined host factors influencing overall susceptibility. These susceptibilities may often include social and psychological factors in addition to recognized environmental factors. These factors may be operating at the level of the individual, the family, the community, or some other broad social grouping. Although this combination will differ from one individual to another, by current definitions and classifications of disease, many individuals may appear to have the same illness. Integration of knowledge of all these divergent areas may provide the foundation for earlier detection of high-risk individuals and could lead to more effective measures of prevention and treatment in coming years.

In 2000, Childs and Valle wrote:

> *The signs and symptoms of a patient today may well have been forged in the developmental and maturational matrix of the past. And in making that characterization, we discern the individuality and heterogeneity of that which we give the name of a disease. ...*
>
> *In medicine we have trouble accepting this kind of individuality. When we see a patient, we think first of the name of a disease and then of the*

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variation expressed in the patient. This way of thinking is typological, and is to be distinguished from "population" thinking in which a population, say, of patients with the "same" disease, consists of variable individuals.[62]

Dalton and Friend published a schematic presentation of the cyclical nature of the process of incorporating new knowledge into therapies that are individualized for each patient (Fig. 16.13) and the process is described in the caption to this figure.[63] Although this approach has great potential, its benefits have not yet been extensively realized in the treatment of most complex diseases. However, new technologies at the molecular and genetic levels are likely to have profound effects on health care and on the development of "*personalized medicine*," which will include new approaches to disease prevention and treatment of disease that will be made possible by technical advances and by the integration of new information derived from different biologic and sociologic disciplines.

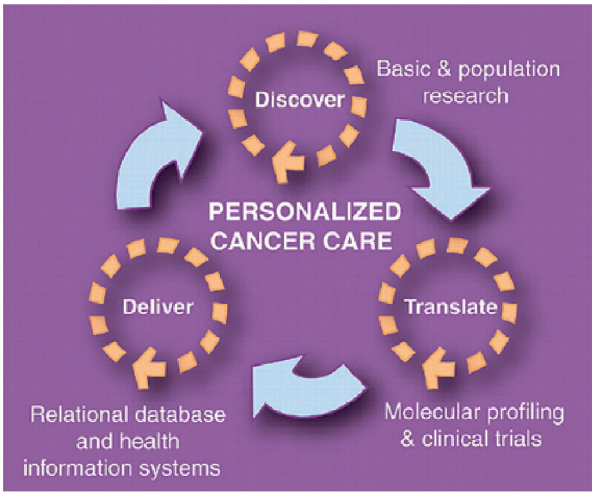

Fig. 16.13 Personalized cancer care as a continuous cycle. The cycle starts with the discovery of specific molecular alterations in tumors that are then linked to specific patient outcomes in clinical trials. The ability to capture molecular profiles and clinical information at the level of individual patients allows translation of the information into more personalized cancer care. Available relational databases and health information systems ensure more informed delivery of cancer therapies to future patients; it can also guide the discovery of new therapies. (From Dalton WS, Friend SH. Cancer biomarkers—an invitation to the table. *Science.* 2006;312:1165–1168.)

CONCLUSION

This chapter has described some of the epidemiologic approaches used to assess the relative contributions of genetic and environmental factors in causing human disease. The link of epidemiology and genetics has become increasingly recognized, and a field called *genetic epidemiology* has emerged.[19] Excellent discussions have been published regarding the impact of the genomic era on epidemiologic research.[64,65]

Most epidemiologic studies are directed at identifying environmental factors in controlling the risk of disease, but when designing and conducting studies and interpreting their results, it is important to bear in mind that individuals in epidemiologic studies differ not only in environmental exposures but also in their genetic makeup, and this too influences risk. When appropriate, epidemiologic studies of risk factors, including case-control and other study designs, should be expanded to include gathering family histories and obtaining biologic samples whenever possible. Incorporating genetic advances and genetic markers into epidemiologic studies is proving increasingly valuable in identifying high-risk subgroups and tailoring therapies specific to the individual. They are likely to become increasingly important in improving disease prevention in the future.

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REVIEW QUESTIONS FOR CHAPTER 16

1. *If a greater proportion of monozygotic twin pairs are found to be concordant for a certain disease than are dizygotic twin pairs, the observation suggests that the disease is most likely caused by:*
   - **a.** Exclusively environmental factors
   - **b.** Exclusively genetic factors
   - **c.** Hereditary factors almost exclusively, with some nonhereditary factors possibly playing a role
   - **d.** Environmental and genetic factors almost equally
   - **e.** Gender differences in monozygotic twins
2. *When the incidence of a disease in adopted children is studied and compared with its incidence in biologic relatives and in adoptive relatives, all of the following are relevant concerns except:*
   - **a.** Age at onset
   - **b.** Amount of contact maintained by the adoptee with their biologic parents
   - **c.** Marital status of the biologic parents
   - **d.** Selection factors relating to who is adopted and who is not
   - **e.** *c* and *d*

Question 3 is based on the information given below:
In a familial study of schizophrenia, the following concordance rates were observed within various pairs of relatives:

Pair	Concordance Rate (%)
Husband–wife	5
Parent–child	40
Monozygotic twins	65
Dizygotic twins	42
Ordinary siblings	40

3. *A reasonable conclusion to be drawn from these data is:*
   - **a.** Genetic factors are unimportant in the etiology of schizophrenia
   - **b.** The data suggest a potentially important genetic component
   - **c.** The incidence of schizophrenia within relative pairs is highest in monozygotic twins
   - **d.** The prevalence of schizophrenia within relative pairs is highest in monozygotic twins
   - **e.** Twins are less likely to have schizophrenia than are ordinary siblings

Question 4 is based on the information given below:
In a study of Japanese migrants to the United States, the following standardized mortality ratios (SMRs) were found for disease X:

Group	Standardized Mortality Ratio
Native Japanese living in Japan	100
Japanese migrants	105
Children of Japanese ancestry	108
United States White population	591

4. *These findings suggest that:*
   - **a.** Environmental factors are the major determinants of these SMRs
   - **b.** Genetic factors are the major determinants of these SMRs
   - **c.** Environmental factors associated with the migrant culture are probably involved
   - **d.** Migrants are highly selected and are nonrepresentative of the population in their native country
   - **e.** International differences in coding death certificates for disease X are an important determinant of these SMRs
5. *If an association is found between the incidence of a disease and a certain genetically determined characteristic:*
   - **a.** The disease is clearly genetic in origin
   - **b.** Genetic factors are at least implicated in all cases of the disease
   - **c.** Genetic factors are implicated in at least some cases of the disease
   - **d.** A role for environmental factors is excluded
   - **e.** Expression of the disease is likely to be unavoidable

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GLOSSARY OF GENETIC TERMS FOR CHAPTER 16

Term	Definition
Agnostic approach	An agnostic approach in genetic epidemiology is where you evaluate the entire genome without a preconceived plan for where the associated variants may exist (i.e., not targeting a specific gene or set of genes). This approach allows you to find new discoveries that are not limited to existing knowledge about pathway or biology.
Allele	An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Though the term allele was originally used to describe variation among genes, it now also refers to variation among noncoding DNA sequences.
Autism	Autism is a developmental brain disorder characterized by impaired social interactions, communication problems, and repetitive behaviors. Symptoms usually appear before the age of 3 years. The exact cause of autism is not known; however, it is likely influenced by genetics. Autism is one of a group of related developmental disorders called autism spectrum disorders (ASDs). Other ASDs include Asperger syndrome and Rett syndrome.
Autosomal Dominant	Autosomal dominance is a pattern of inheritance characteristic of some genetic diseases. "Autosomal" means that the gene in question is located on one of the numbered, or nonsex, chromosomes. "Dominant" means that a single copy of the disease-associated mutation is enough to cause the disease. This is in contrast to a recessive disorder, where two copies of the mutation are needed to cause the disease. Huntington disease is a common example of an autosomal dominant genetic disorder.
Candidate Gene	A candidate gene is a gene whose chromosomal location is associated with a particular disease or other phenotype. Because of its location, the gene is suspected of causing the disease or other phenotype.
Carrier	A carrier is an individual who carries and is capable of passing on a genetic mutation associated with a disease and may or may not display disease symptoms. Carriers are associated with diseases inherited as recessive traits. In order to have the disease, an individual must have inherited mutated alleles from both parents. An individual having one normal allele and one mutated allele does not have the disease. Two carriers may produce children with the disease.
Carrier Screening	Carrier screening is a type of genetic testing performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children. A carrier for a genetic disorder has inherited one normal and one abnormal allele for a gene associated with the disorder. A child must inherit two abnormal alleles in order for symptoms to appear. Prospective parents with a family history of a genetic disorder are candidates for carrier screening.
Chromosome	A chromosome is an organized package of DNA found in the nucleus of the cell. Different organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes—22 pairs of numbered chromosomes, called autosomes, and one pair of sex chromosomes, X and Y. Each parent contributes one chromosome to each pair so that offspring get half of their chromosomes from their mother and half from their father.
Complex Disease	A complex disease is caused by the interaction of multiple genes and environmental factors. Complex diseases are also called multifactorial. Examples of complex diseases include cancer and heart disease.
Deletion	Deletion is a type of mutation involving the loss of genetic material. It can be small, involving a single missing DNA base pair; or large, involving a piece of a chromosome.

Term	Definition
DNA (Deoxyribonucleic Acid)	DNA is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases—adenine (A), cytosine (C), guanine (G), and thymine (T). The two strands are held together by bonds between the bases: adenine bonds with thymine, and cytosine bonds with guanine. The sequences of the bases along the backbones serve as instructions for assembling protein and RNA molecules.
DNA Sequencing	DNA sequencing is a laboratory technique used to determine the exact sequence of bases (A, C, G, and T) in a DNA molecule. The DNA base sequence carries the information a cell needs to assemble protein and RNA molecules. DNA sequence information is important to scientists investigating the functions of genes. The technology of DNA sequencing was made faster and less expensive as a part of the Human Genome Project.
Dominant	Dominant refers to the relationship between two versions of a gene. Individuals receive two versions of each gene, known as alleles, from each parent. If the alleles of a gene are different, one allele will be expressed; it is the dominant gene. The effect of the other allele, called recessive, is masked.
Fraternal Twins	Fraternal twins are also dizygotic twins. They result from the fertilization of two separate eggs during the same pregnancy. Fraternal twins may be of the same or different sexes. They share half of their genes just like any other siblings. In contrast, twins that result from the fertilization of a single egg that then splits in two are called monozygotic, or identical, twins. Identical twins share all of their genes and are always the same sex.
Gene	The gene is the basic physical unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify traits. Genes are arranged, one after another, on structures called chromosomes. A chromosome contains a single, long DNA molecule, only a portion of which corresponds to a single gene. Humans have approximately 20,000 genes arranged on their chromosomes.
Gene Environment Interaction	Gene environment interaction is an influence on the expression of a trait that results from the interplay between genes and the environment. Some traits are strongly influenced by genes, while other traits are strongly influenced by the environment. However, most traits are influenced by one or more genes interacting in complex ways with the environment.
Gene Mapping	Gene mapping is the process of establishing the locations of genes on the chromosomes. Early gene maps used linkage analysis. The closer two genes are to each other on the chromosome, the more likely it is that they will be inherited together. By following inheritance patterns, the relative positions of genes can be determined. More recently, scientists have used recombinant DNA (rDNA) techniques to establish the actual physical locations of genes on the chromosomes.
Genetic Counseling	Genetic counseling is the professional interaction between a health care provider with specialized knowledge of genetics and an individual or family. The genetic counselor determines whether a condition in the family may be genetic and estimates the chances that another relative may be affected. Genetic counselors also offer and interpret genetic tests that may help to estimate the risk of disease. The genetic counselor conveys information in an effort to address concerns of the client and provides psychological counseling to help families adapt to their condition or risk.
Genetic Epidemiology	Genetic epidemiology is a relatively new medical discipline that seeks to understand how genetic factors interact with the environment in the context of disease in populations. Areas of study include the causes of inherited disease and its distribution and control.
Genetic Map	A genetic map is a type of chromosome map that shows the relative locations of genes and other important features. The map is based on the idea of linkage, which means that the closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together. By following inheritance patterns, the relative locations of genes along the chromosome are established.

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Term	Definition
Genetic Marker	A genetic marker is a DNA sequence with a known physical location on a chromosome. Genetic markers can help link an inherited disease with the responsible gene. DNA segments close to each other on a chromosome tend to be inherited together. Genetic markers are used to track the inheritance of a nearby gene that has not yet been identified, but whose approximate location is known. The genetic marker itself may be a part of a gene or may have no known function.
Genetic Screening	Genetic screening is the process of testing a population for a genetic disease in order to identify a subgroup of people who either have the disease or the potential to pass it on to their offspring.
Genome	The genome is the entire set of genetic instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cells' mitochondria. Each set of 23 chromosomes contains approximately 3.1 billion bases of DNA sequence.
Genome-Wide Association Studies (GWAS)	A genome-wide association study (GWAS) is an approach used in genetics research to associate specific genetic variations with particular diseases. The method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease. Once such genetic markers are identified, they can be used to understand how genes contribute to the disease and develop better prevention and treatment strategies.
Genomics	Genomics refers to the study of the entire genome of an organism, whereas genetics refers to the study of a particular gene.
Genotype	A genotype is an individual's collection of genes. The term also can refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype.
Germ Line	A germ line is the sex cells (eggs and sperm) that are used by sexually reproducing organisms to pass on genes from generation to generation. Egg and sperm cells are called germ cells, in contrast to the other cells of the body that are called somatic cells.
Heterozygous	Heterozygous refers to having inherited different forms of a particular gene from each parent. A heterozygous genotype stands in contrast to a homozygous genotype, where an individual inherits identical forms of a particular gene from each parent.
Homozygous	Homozygous is a genetic condition where an individual inherits the same alleles for a particular gene from both parents.
Identical Twins	Identical twins are also known as monozygotic twins. They result from the fertilization of a single egg that splits in two. Identical twins share all of their genes and are always of the same sex. In contrast, fraternal, or dizygotic, twins result from the fertilization of two separate eggs during the same pregnancy. They share half of their genes, just like any other siblings. Fraternal twins can be of the same or different sexes.
Inherited	An inherited trait is one that is genetically determined. Inherited traits are passed from parent to offspring according to the rules of Mendelian genetics. Most traits are not strictly determined by genes, but rather are influenced by both genes and environment.
Linkage	Linkage is the close association of genes or other DNA sequences on the same chromosome. The closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together.
Locus	A locus is the specific physical location of a gene or other DNA sequence on a chromosome, like a genetic street address. The plural of locus is "loci."
Mapping	Mapping is the process of making a representative diagram cataloging the genes and other features of a chromosome and showing their relative locations. Cytogenetic maps are made using photomicrographs of chromosomes stained to reveal structural variations. Genetic maps use the idea of linkage to estimate the relative locations of genes. Physical maps, made using recombinant DNA (rDNA) technology, show the actual physical locations of landmarks along a chromosome.

Term	Definition
Mendel, Johann (Gregor)	Gregor Mendel was an Austrian monk who, in the 19th century, worked out the basic laws of inheritance, even before the term "gene" had been coined. In his monastery garden, Mendel performed thousands of crosses with garden peas. Mendel is considered the founder of the science of genetics.
Mendelian Inheritance	Mendelian inheritance refers to patterns of inheritance that are characteristic of organisms that reproduce sexually. The Austrian monk Gregor Mendel performed thousands of crosses with garden peas at his monastery during the middle of the 19th century. Mendel explained his results by describing two laws of inheritance that introduced the idea of dominant and recessive genes.
Monogenic Disorders or Monogenic Traits	These are disorders or traits that are caused by variation in a single gene, and often follow a familial inheritance pattern. One example is cystic fibrosis.
Mutation	A mutation is a change in a DNA sequence. Mutations can result from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to chemicals called mutagens, or infection by viruses. Germ line mutations occur in the eggs and sperm and can be passed on to offspring, while somatic mutations occur in body cells and are not passed on.
Newborn Screening	Newborn screening is testing performed on newborn babies to detect a wide variety of disorders. Typically, testing is performed on a blood sample obtained from a heel prick when the baby is 2 or 3 days old. In the United States, newborn screening is mandatory for several different genetic disorders, though the exact set of required tests differs from state to state.
Pedigree	A pedigree is a genetic representation of a family tree that diagrams the inheritance of a trait or disease though several generations. The pedigree shows the relationships between family members and indicates which individuals express or silently carry the trait in question.
Phenotype	A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while other traits are largely determined by environmental factors.
Polygenic Trait	A polygenic trait is one whose phenotype is influenced by more than one gene. Traits that display a continuous distribution, such as height or skin color, are polygenic. The inheritance of polygenic traits does not show the phenotypic ratios characteristic of Mendelian inheritance, though each of the genes contributing to the trait is inherited as described by Gregor Mendel. Many polygenic traits are also influenced by the environment and are called multifactorial.
Polymorphism	Polymorphism involves one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair. Polymorphisms can also be much larger in size and involve long stretches of DNA.
Sex Linked	Sex linked is a trait in which a gene is located on a sex chromosome. In humans, the term generally refers to traits that are influenced by genes on the X chromosome. This is because the X chromosome is large and contains many more genes than the smaller Y chromosome. In a sex-linked disease, it is usually males who are affected because they have a single copy of X chromosome that carries the mutation. In females, the effect of the mutation may be masked by the second healthy copy of the X chromosome.
Single Nucleotide Polymorphisms (SNPs)	SNPs are a type of polymorphism involving variation of a single base pair. Scientists are studying how SNPs in the human genome correlate with disease, drug response, and other phenotypes.
Trait	A trait is a specific characteristic of an organism. Traits can be determined by genes or the environment, or more commonly by interactions between them. The genetic contribution to a trait is called the genotype. The outward expression of the genotype is called the phenotype.
X-Linked	X-linked is a trait where a gene is located on the X chromosome. Humans and other mammals have two sex chromosomes, the X and the Y. In an X-linked or sex-linked disease, it is usually males that are affected because they have a single copy of the X chromosome that carries the mutation. In females, the effect of the mutation may be masked by the second healthy copy of the X chromosome.

Data from National Human Genome Research Institute. Glossary of genetic terms. https://www.genome.gov/glossary/index.cfm. Accessed December 10, 2017.

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SECTION III

Applying Epidemiology to Evaluation and Policy

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17

Using Epidemiology to Evaluate Health Services

LEARNING OBJECTIVES

- To distinguish measures of process from measures of outcome, and to discuss some commonly used measures of outcome in health services research.
- To define efficacy, effectiveness, and efficiency in the context of health services.
- To compare and contrast epidemiologic studies of disease etiology with epidemiologic studies evaluating health services.
- To discuss outcomes research in the context of ecologic data, and to present some potential biases in epidemiologic studies that emerge when evaluating health services using group-level data.
- To describe some possible study designs that can be used to evaluate health services using individual-level data, including randomized and nonrandomized designs.

Perhaps the earliest example of an evaluation is the description of creation given in the book of Genesis 1:1–4, which is shown in the original Hebrew in Fig. 17.1. Translated, with the addition of a few subheadings, it reads as follows:

> *BASELINE DATA*
> *In the beginning God created the heaven and the earth. And the earth was unformed and void and darkness was on the face of the deep.*
>
> *IMPLEMENTATION OF THE PROGRAM*
> *And God said, "Let there be light." And there was light.*
>
> *EVALUATION OF THE PROGRAM*
> *And God saw the light, that it was good.*
>
> *FURTHER PROGRAM ACTIVITIES*
> *And God divided the light from the darkness.*

This excerpt includes all of the basic components of the process of evaluation: baseline data, implementation of the program, evaluation of the program, and implementation of new program activities on the basis of the results of the evaluation. However, two problems arise in this description. First, we are not given the precise criteria that were used to determine whether or how the program was "good"; we are told only that God saw that it was good (which, in hindsight, may be sufficient). Second, this evaluation exemplifies a frequently observed problem: the program director is assessing his own program. Both conscious and subconscious biases can arise in evaluation. Furthermore, even if the program director administers the program superbly, he or she may not necessarily have the specific skills that are needed to conduct a methodologically rigorous evaluation of the program.

Dr. Wade Hampton Frost, a leader in epidemiology in the early part of the 20th century and the first Chair of Epidemiology at Johns Hopkins, addressed the use of epidemiology in the evaluation of public health programs in a presentation to the American Public Health Association in 1925.[1] He wrote, in part, as follows:

> *The health officer occupies the position of an agent to whom the public entrusts certain of its resources in public money and cooperation, to be so invested that they may yield the best returns in health; and in discharging the responsibilities of this position he is expected to follow the same general principles of*

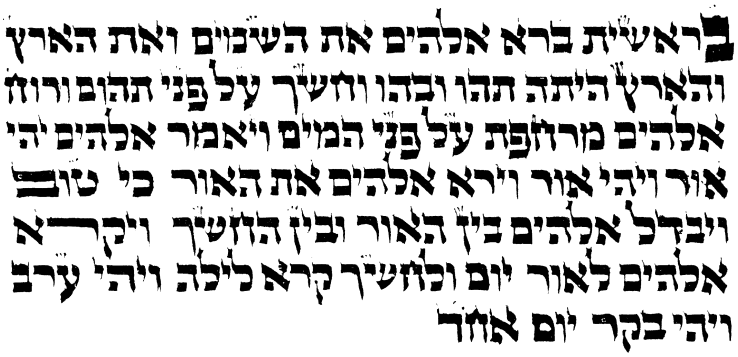
בראשית ברא אלהים את השמים ואת הארץ
והארץ היתה תהו ובהו וחשך על פני תהום ורוח
אלהים מרחפת על פני המים ויאמר אלהים יהי
אור ויהי אור וירא אלהים את האור כי טוב
ויבדל אלהים בין האור ובין החשך ויקרא
אלהים לאור יום ולחשך קרא לילה ויהי ערב
ויהי בקר יום אחד

Fig. 17.1 The earliest known evaluation (Genesis 1:1–4).

procedure as would be a fiscal agent under like circumstances. ...

Since his capital comes entirely from the public, it is reasonable to expect that he will be prepared to explain to the public his reasons for making each investment, and to give them some estimate of the returns which he expects. Nor can he consider it unreasonable if the public should wish to have an accounting from time to time, to know what returns are actually being received and how they check with the advance estimates which he has given them. Certainly any fiscal agent would expect to have his judgment thus checked and to gain or lose his clients' confidence in proportion as his estimates were verified or not.

However, as to such accounting, the health officer finds himself in a difficult and possibly embarrassing position, for while he may give a fairly exact statement of how much money and effort he has put into each of his several activities, he can rarely if ever give an equally exact or simple accounting of the returns from these investments considered separately and individually. This, to be sure, is not altogether his fault. It is due primarily to the character of the dividends from public health endeavor, and the manner in which they are distributed. They are not received in separate installments of a uniform currency, each docketed as to its source and recorded as received; but come irregularly from day to day, distributed to unidentified individuals throughout the community, who are not individually conscious of having received them. They are positive benefits in added life and improved health, but the only record ordinarily kept in morbidity and mortality statistics is the partial and negative record of death and of illness from certain clearly defined types of disease, chiefly the more acute communicable diseases, which constitute only a fraction of the total morbidity.[1]

Dr. Charles V. Chapin commented on Frost's presentation:

Dr. Frost's earnest demand that the procedures of preventive medicine be placed on a firm scientific basis is well timed. Indeed, it would have been opportune at any time during the past 40 years and, it is to be feared, will be equally needed for 40 years to come.[2]

Chapin clearly underestimated the number of years; the need remains as critical today, some 100 years later, as it was in 1925.

STUDIES OF PROCESS AND OUTCOME

Avedis Donabedian is widely regarded as the author of the seminal work on creating a framework of examining health services in relation to the quality assurance of healthcare services. He identified three important factors simultaneously at play: (1) structure, (2) process, and (3) outcome. Structure relates to the physical locations where care is provided, the personnel, equipment, and financing. We will restrict our discussion here to the remaining two components, process and outcome.

Studies of Process

At the outset, we should distinguish between process and outcome studies. *Process* means that we decide what constitutes the components of good care, services, or preventive actions. Such a decision may first be made by an expert panel. We can then assess a clinic or health care provider, by reviewing relevant records or by direct

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observation, and determine to what extent the care provided meets established and accepted criteria. For example, in primary care we can determine what percentage of patients have had their blood pressure measured. The problem with such process measures is that they do not indicate whether the patient is better off; for example, monitoring blood pressure does not ensure that the patient's blood pressure is under control or that the patient will consistently take antihypertensive medications as they are prescribed. Second, because process assessments are often based on expert opinion, the criteria used in process evaluations may change over time as expert opinion changes. For example, in the 1940s, the accepted standard of care for premature infants required that such infants be placed in 100% oxygen. Incubators were monitored to be sure that such levels were maintained. However, when research demonstrated that high oxygen concentration played a major role in producing retrolental fibroplasia—a form of blindness in children who had been born prematurely—high concentrations of oxygen were subsequently deemed unacceptable.

Studies of Outcome

Given the limitations of process studies, the remainder of this chapter focuses on outcome measures. *Outcome* denotes whether or not a patient (or a community at large) benefits from the medical care provided. Health outcomes are frequently considered the domain of epidemiology. Although such measures have traditionally been mortality and morbidity, interest in outcomes research in recent years has expanded the measures of interest to include patient satisfaction and well-being, quality of life, degree of dependence and disability, and similar measures.

EFFICACY, EFFECTIVENESS, AND EFFICIENCY

Three terms that are often encountered in the literature dealing with evaluation of health services are *efficacy*, *effectiveness*, and *efficiency*. These terms are often used in association with the findings from randomized trials.

Efficacy

Does the agent or intervention "work" under ideal "laboratory" conditions? We test a new drug in a group of patients who have agreed to be hospitalized and who are observed as they take their therapy. Or a vaccine is tested in a group of consenting subjects. Thus, efficacy is a measure in a situation in which all conditions are controlled to maximize the effect of the agent. Generally, "ideal" conditions are those that occur in testing a new agent of intervention using a randomized trial.

Effectiveness

If we administer the agent in a "real-life" situation, is it effective? For example, when a vaccine is tested in a community, many individuals may not come in to be vaccinated. Or an oral medication may have such an undesirable taste that no one will take it (so that it will prove ineffective), despite the fact that under controlled conditions, when compliance was ensured, the drug was shown to be efficacious.

Efficiency

If an agent is shown to be effective, what is the cost–benefit ratio? Is it possible to achieve our goals in a less expensive and better way? Cost includes not only money, but also discomfort, pain, absenteeism, disability, and social stigma.

If a health care measure has not been demonstrated to be effective, there is little point looking at efficiency, for if it is not effective, the best alternative is not to use it at all. At times, of course, political and societal pressures may drive a program even if it is not effective (an often-cited example is DARE—Drug Abuse Resistance Education, which has never been shown to have an impact on adolescent and young adult drug use). However, this chapter will focus only on the science of evaluation and specifically on the issue of effectiveness in evaluating health services.

MEASURES OF OUTCOME

If the efficacy of a measure has been shown to be effective—that is, if the methods of prevention and intervention that are of interest have been shown to work—we can then turn to evaluating effectiveness. What guidelines should we use in selecting an appropriate outcome measure to serve as an index of effectiveness? First, the measure must be clearly *quantifiable*; that is, we must be able to express its effect in quantitative terms. Second, the measure of outcome should be relatively *easy to define* and there should be agreement on how it should be measured. If the measure is to be used in a

population study, we certainly would not want to depend on an invasive procedure to assess any benefits. Third, the measure selected should lend itself to *standardization* for study purposes. Fourth, the population served (and the comparison population) must be *at risk* for the same condition for which an intervention is being evaluated. For example, it would obviously make little sense to test the effectiveness of a sickle cell screening program in a White population in North America (as sickle cell disease primarily affects Black Americans).

The type of health outcome end point that we select clearly should depend on the question that we are asking. Although this may seem self-evident, it is not always immediately apparent. Box 17.1 shows possible end points in evaluating the effectiveness of a vaccine program. Whatever outcome we select should be explicitly stated so that others reading the report of our findings will be able to make their own judgments regarding the appropriateness of the measure selected and the quality of the data we use for the evaluation. Whether the measure we have selected is indeed an appropriate one depends on clinical and public health aspects of the disease or health condition in question.

Box 17.2 shows possible choices of measures for assessing the effectiveness of a throat culture program in children. Measures of volume of services provided, numbers of cultures taken, and number of clinic visits have been traditionally used because they are relatively easy to count and are helpful in justifying requests for budgetary increases for the program in the following year. However, such measures are all process measures and tell us nothing about the effectiveness of the intervention. We therefore move to other possibilities listed in this box. Again, the most appropriate measures should depend on the question being asked. The question must be specific. It is not enough just to ask how good the program is.

BOX 17.1 Some Possible End Points for Measuring the Success of a Vaccine Program

1. Number (or proportion) of people immunized
2. Number (or proportion) of people at (high) risk who are immunized
3. Number (or proportion) of people immunized who show serologic response
4. Number (or proportion) of people immunized and later exposed in whom clinical disease does not develop
5. Number (or proportion) of people immunized and later exposed in whom clinical or subclinical disease does not develop

BOX 17.2 Some Possible End Points for Measuring Success of a Throat Culture Program

1. Number of cultures taken (symptomatic or asymptomatic)
2. Number (or proportion) of cultures positive for streptococcal infection
3. Number (or proportion) of persons with positive cultures for whom medical care is obtained
4. Number (or proportion) of persons with positive cultures for whom proper treatment is prescribed and taken
5. Number (or proportion) of positive cultures followed by a relapse

COMPARING EPIDEMIOLOGIC STUDIES OF DISEASE ETIOLOGY AND EPIDEMIOLOGIC RESEARCH EVALUATING EFFECTIVENESS OF HEALTH SERVICES

In classic epidemiologic studies of disease etiology, we examine the possible relationship between a putative cause (the independent variable or "exposure") and an adverse health effect or effects (the dependent variable or "outcome"). In doing so, we take into account other factors, including health care that may modify the relationship or confound it (Fig. 17.2A). In health services research, we focus on the health service as the independent variable (the "exposure"), with a reduction in adverse health effects as the anticipated outcome (the "dependent" variable) if the modality of care is effective. In this situation, environmental and other factors that may influence the relationship are also considered (see Fig. 17.2B). Thus, both etiologic epidemiologic research and health services research address the possible relationship between an independent variable and a dependent variable, and the influence of other factors on the relationship. Therefore, it is not surprising that many of the study designs discussed are common to both epidemiologic and health services research, as are the methodologic problems and potential biases that may characterize these types of studies.

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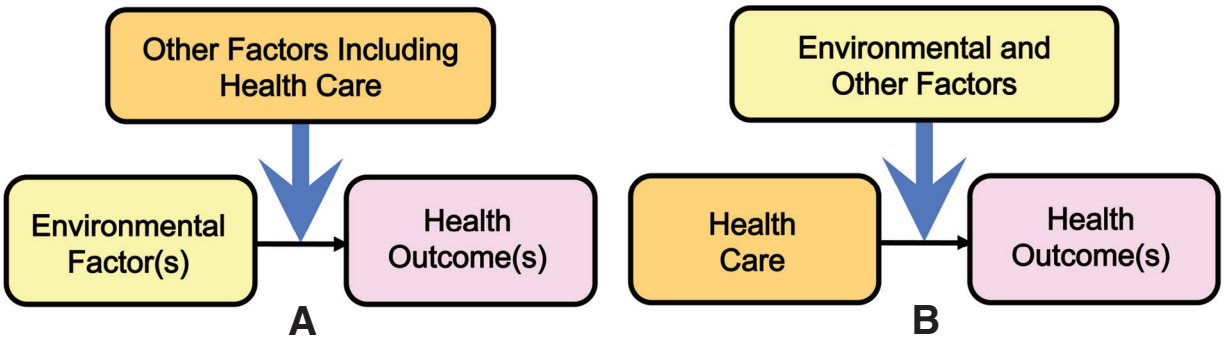

Fig. 17.2 **(A)** Classic epidemiologic research into etiology, taking into account the possible influence of other factors, including health care. **(B)** Classic health services research into effectiveness, taking into account the possible influence of environmental and other factors.

EVALUATION USING GROUP DATA

Regularly available data, such as mortality data and hospitalization data, are often used in evaluation studies. Such data can be obtained from different sources, and such sources may differ in important ways. For example, Fig. 17.3 shows the changes in the estimated proportion of the US population with influenza-like illness (ILI) over time—*trends*—using different data sources: sentinel surveillance sites overseen by the Centers for Disease Control and Prevention (CDC) and Flu Near You.[3]

Although the trends are fairly similar in this time period, we can see that the estimates vary. This is potentially attributed to the varying methodology of data collection of each data source. The CDC generates its data from over 2,700 health care centers that capture over 30 million patient visits each year. Flu Near You uses data entered by internet users volunteering information, not necessarily physicians, to report on a weekly basis whether they, or their family members, have ILI symptoms. It is possible that not all individuals who develop ILI symptoms will seek medical care, and hence are not captured by the CDC data, but they may perform a Google search for ways to alleviate ILI symptoms, for example. Since Flu Near You solely depends on voluntary self-report of ILI symptoms it might well underestimate prevalence. In a recent flu season, then New York State Governor Andrew M. Cuomo declared a Public Health Emergency in response to a severe flu season. It was suggested that this might have prompted numerous searches on Google by individuals who are

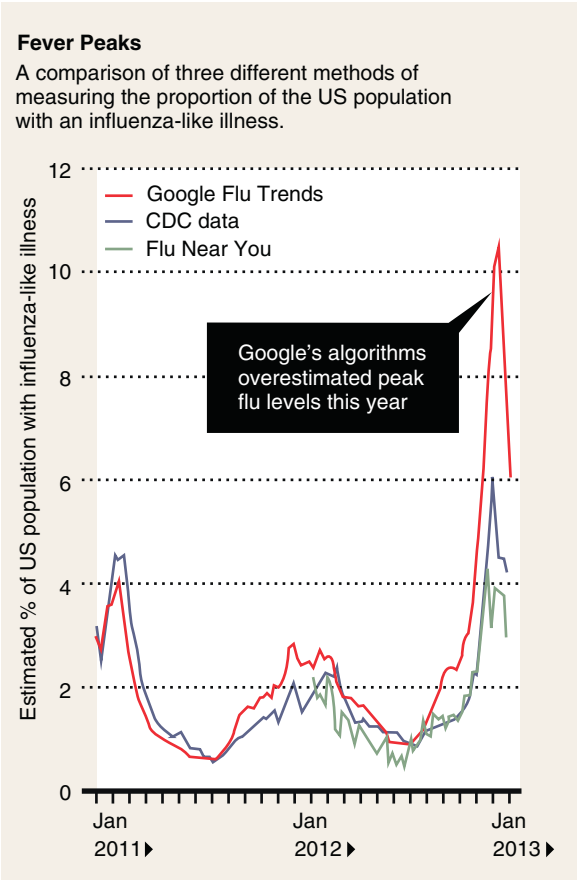

Fig. 17.3 Estimated proportion of US population with influenza-like illness January 2011–13. *CDC,* Centers for Disease Control and Prevention. (From Butler D. When Google got flu wrong. *Nature.* 2013;494:155–156.)

not actually suffering from ILI symptoms, which in turn could have triggered the spike that we see in the figure.

Outcomes Research

The term *outcomes research* has been increasingly used to denote studies comparing the effects of two or more health care interventions or modalities—such as treatments, forms of health care organization, volume of procedures conducted per facility, or type and extent of insurance coverage and provider reimbursement—on health or economic outcomes. The health end points may include morbidity and mortality as well as measures of quality of life, functional status, and patient perceptions of their health status, including symptom recognition and patient-reported satisfaction. Economic measures may reflect direct or indirect costs, and can include hospitalization rates, rehospitalization for the same condition within 30 days of discharge, outpatient and emergency room visits, lost days of work, childcare requirements and school absences, and days of restricted activity. Consequently, epidemiology is one of several disciplines needed in outcomes research.

Outcomes research often uses data from large data sets that were derived from large populations. Although in recent years some of the large data sets have been developed from cohorts that were originally set up for different research purposes, many of the data sets used were often originally initiated for administrative or fiscal purposes, rather than for any research goals. Often several large data sets, each having information on different variables, may be combined or linked (resulting in "meta-data") in order to have sufficient sample size to explore a question of interest.

With the advent of the electronic medical record (EMR), patient care data are increasingly available to the epidemiology and health services research communities. The purpose of the EMR is to provide health care providers all the information pertaining to individual patients—findings from office visits, utilization of preventive services, prescribed medications, procedures, radiologic findings, laboratory test results—continuously over time (i.e., prospectively). However, the purpose of the EMR is not to serve as a research base but to direct patient care. Harnessing the EMR to evaluate health services research questions has great promise, but to date it has proven difficult to use and the methods to maximize its potential are still being developed and tested in the field.

The advantages of using large data sets (sometimes referred to as "big data") are that the data refer to real-world populations, and the issue of "representativeness" or "generalizability" is minimized. In addition, since the data sets exist at the time the research is initiated, analysis can generally be completed fairly quickly, and results generated relatively rapidly. Moreover, given the large data sets used, sample size is not usually a problem except when smaller subgroups are examined. As an example, Medicare claims data allow stratification of relatively small groups with adequate sample size for statistical analysis. Given these considerations, the costs of using existing data sets are generally lower than the costs of primary data collection. Health insurance claims data are another example of large data that can be used for outcomes analysis.

The disadvantages are that, since the data were often initially gathered for patient care, billing, and administrative purposes, they may not be well suited for research purposes and for answering the specific research question addressed in the study. Even when the data were originally gathered for research, our knowledge of the area may now be more complete and new research questions may have arisen that were not even conceived of when the original data collection was initiated. In general, data may be incomplete and not have all of the potential confounders that we know are important. Data on the independent and dependent variables may be limited. Data may be missing on clinical details including disease severity and on the details of interventions, and diagnostic coding may be inconsistent across facilities and within facilities over time. Data relating to possible confounders may be inadequate or absent since the research now being conducted was often not even possible when the data were originally generated. Because certain variables that today are considered relevant and important were not included in the original data, investigators may at times create surrogate variables for the missing variables, using certain variables that are included in the data set but that may not directly reflect the variable of interest. However, such surrogate variables vary in the extent to which they are an adequate measure of the missing variable of interest. For all these reasons, the validity of the conclusions reached may therefore be in doubt.

Another important problem that may arise with large data sets is that because the necessary variables may be absent in the available data set, the investigator may

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consciously or subconsciously change from the question they had originally wanted to address to a question that is of lesser interest, but for which the variables that are needed for conducting the study are present in the data set. Thus, rather than the investigator deciding what research question should be addressed, the data set itself may end up determining what questions are asked in the study.

Finally, using large data sets, investigators become progressively more removed from the individuals being studied. Over the years, direct interviews and reviews of patient records have tended to be replaced by the use of large, computerized databases. Using these sources of data, many personal characteristics of the subjects cannot be explored and their relevance to the questions being asked is virtually never assessed.

One area in which existing sources of data are often used in evaluation studies is prenatal care. The problems discussed earlier are exemplified by the use of birth certificates. These documents are often used because they are easily accessible and provide certain medical care data, such as the trimester in which prenatal care was begun. However, birth certificates for women with high-risk pregnancies have missing data more often than those for women with low-risk pregnancies. The quality of the data provided on birth certificates also may differ regionally and internationally, which may complicate any comparisons that are made.

An example of outcomes research using large data sets is a study by Bongiovanni et al. of Medicare beneficiaries in the United States.[4] Since Medicare health coverage is provided to virtually all elderly (ages 65 years and older) individuals in the United States, it is assumed that if a study population is limited to those who have Medicare coverage, financial obstacles to care and other variables such as age, sex, or racial/ethnic subpopulations are held constant among different groups. However, wide disparities remain between blacks and whites in the utilization of many Medicare services. Gabapentinoids are thought of as opioid-sparing medications and can potentially reduce the overprescribing of opioids. In light of professional medical societies to tackle the opioid epidemic, surgeons were encouraged to increase the utilization of other medications and modalities other than opioids. The authors asked the question whether postoperative use of gabapentinoids is increasing, and whether their use is associated with decreased opioid prescribing among older adults. The authors analyzed nationally representative Medicare data, which included 494,922 patients aged 66 or older between 2013 and 2018 who underwent common noncataract surgical procedures. The study found a significant increase in postoperative gabapentinoid prescribing from 2.3% in 2014 to 5.2% in 2018 (Fig. 17.4).

The study revealed variations in prescribing patterns across different surgical procedure types. Orthopedic procedures showed the highest increase in gabapentinoid prescribing, while spinal procedures started with a high prescription rate but did not increase as rapidly (Fig. 17.5). Despite the overall increase in gabapentinoid

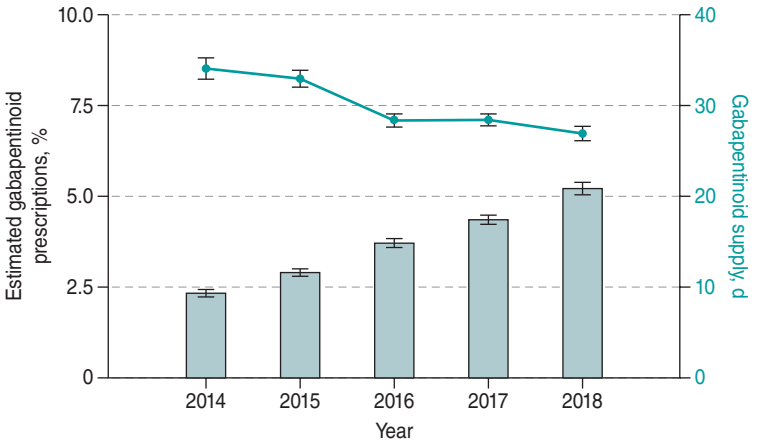

Fig. 17.4 Rate of New Postoperative Gabapentinoid Prescribing Over Time. (From Bongiovanni T, Gan S, Finlayson E, et al. Trends in the use of gabapentinoids and opioids in the postoperative period among older adults. *JAMA Netw Open.* 2023;6(6)).

use, it did not lead to a reduction in the proportion of patients receiving postoperative opioid prescriptions (Fig. 17.6). In the meantime, it is important to highlight the limitations in the use of administrative data sets and the inability to generalize to younger and uninsured individuals. Furthermore, the authors emphasized the inability to generalize the results to patients in skilled nursing facilities, and the possibility of imperfect capture of actual medication use due to the administrative nature of this dataset.

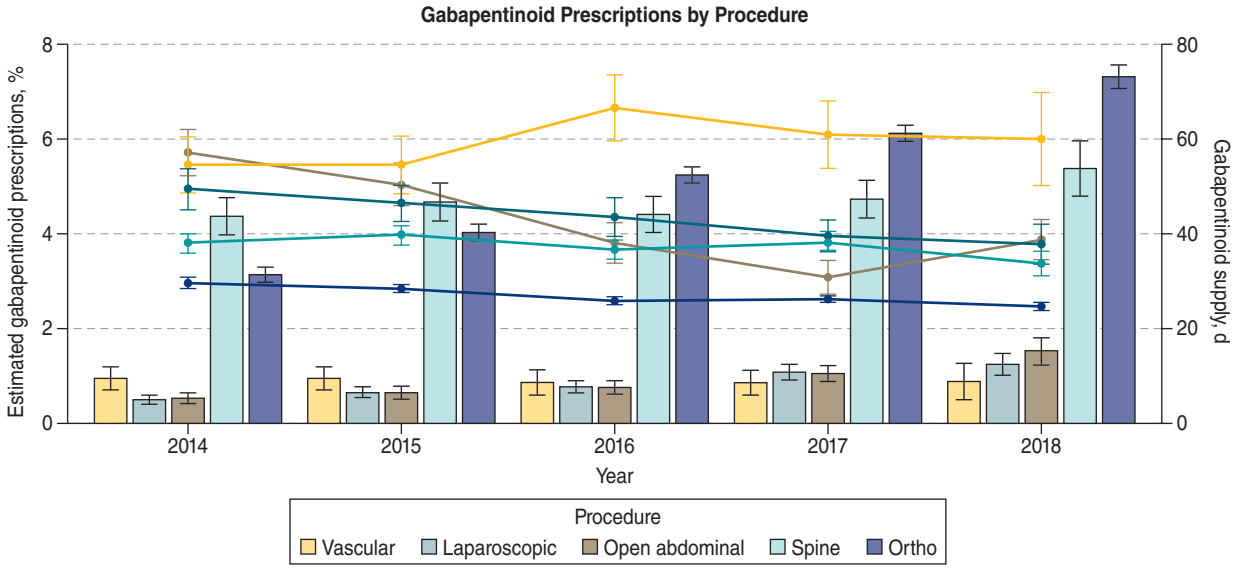

Fig. 17.5 Gabapentinoid Prescriptions by Procedure. (From Bongiovanni, Gan S, Finlayson E, et al. Trends in the use of gabapentinoids and opioids in the postoperative period among older adults. *JAMA Netw Open*. 2023;6(6)).

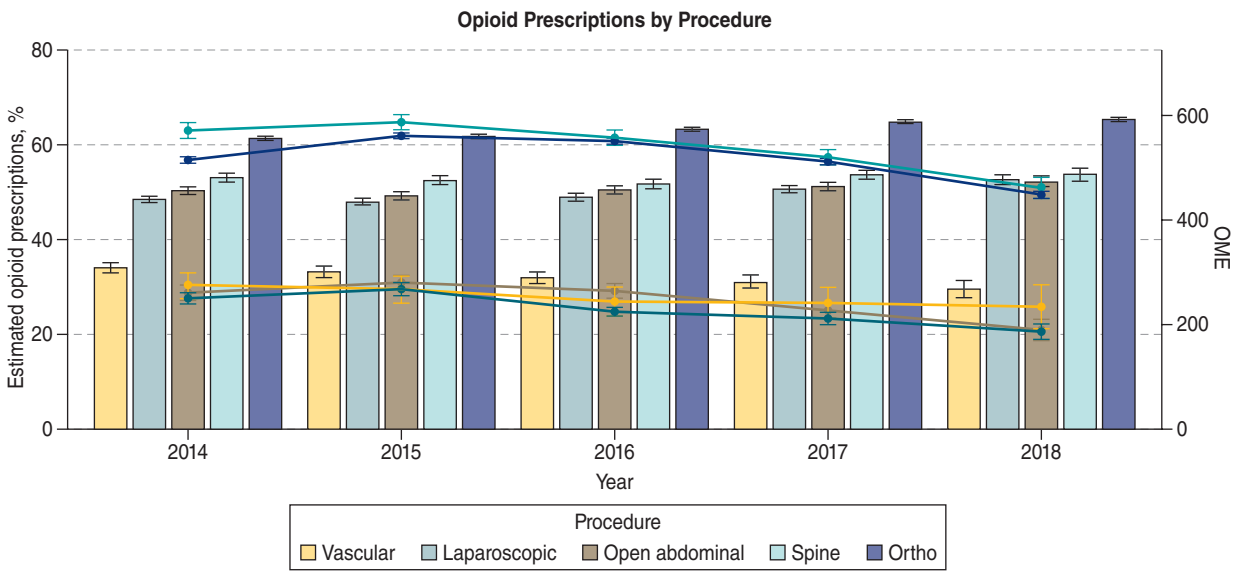

Fig. 17.6 Opioid prescriptions by procedure. (From Bongiovanni T, Gan S, Finlayson E, et al. Trends in the use of gabapentinoids and opioids in the postoperative period among older adults. *JAMA Netw Open*. 2023;6(6)).

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Potential Biases in Evaluating Health Services Using Group Data

Studies evaluating health services using group data are susceptible to many of the biases that characterize etiologic studies, as discussed in Chapter 15. In addition, certain biases are particularly relevant for specific research areas and topics and may be important depending on the specific epidemiologic design selected. For example, studies of the relationship of prenatal care to birth outcomes are prone to several important potential biases. In such studies, the question is whether prenatal care, as measured by the absolute number of prenatal visits, reduces the risk of prematurity and low birth weight. Several potential biases may be introduced into this type of analysis. For example, other things being equal, a woman who delivers prematurely will have fewer prenatal visits (i.e., the pregnancy was shorter so that there was less time in which it was possible for her to "be at risk" for prenatal visits). The result would be an artefactual relationship between fewer prenatal visits and prematurity, only because the gestation was shorter. However, bias can also operate in the other direction. A woman who begins prenatal care in the last trimester of pregnancy will likely not have an early premature delivery, as she has already carried the pregnancy into the last trimester. This would lead to an observed association of fewer prenatal visits with a reduced likelihood of early premature delivery. In addition, women who have had medical complications or a poor pregnancy outcome in a prior pregnancy may be so anxious that they come for more prenatal visits (where problems with the fetus may be detected earlier), and they may also be at greater risk for a poor outcome. Thus, the potential biases can run in one or both directions. If such women are at risk of an outcome that is not amenable to prevention, an apparent association of more prenatal visits with an adverse outcome may be observed.

Finally, prenatal outcome studies based on prenatal care are often biased by self-selection; that is, the women who choose to begin prenatal care early in pregnancy are often better educated and from a higher socioeconomic status, with more positive attitudes toward preventive health care. Thus, a population of women, who are at lower risk for adverse birth outcomes, select themselves for earlier prenatal care. The result is a potential for an apparent association of early prenatal care with lower risk of adverse pregnancy outcome, even if the care itself is without any true health benefit.

Two Indices Used in Ecologic Studies of Health Services

One index in evaluating health services that uses ecologic studies is avoidable mortality. *Avoidable mortality* analyses assume that the rate of "avoidable deaths" should vary inversely with the availability, accessibility, and quality of medical care in different geographic regions. The UK Office for National Statistics defines avoidable mortality as:

> *Avoidable deaths are all those defined as preventable, amenable, or both, where each death is counted only once. Where a cause of death falls within both the preventable and amenable definition, all deaths from that cause are counted in both categories when they are presented separately.*[5]

Conditions include tuberculosis, hepatitis C, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), selected malignant neoplasms, substance use disorders, cardiovascular and respiratory diseases, unintentional and intentional injuries, among others.

Ideally, avoidable mortality would serve as a measure of the accessibility, adequacy, and effectiveness of care in a geographic area. Deaths from HIV/AIDS will be less frequent in communities with ample, friendly, and convenient HIV testing and counseling and high-quality AIDS service organizations, often found in urban areas. In rural areas, such services may be less accessible, and diagnoses may only be made when a patient presents with an AIDS-defining illness. Thus, patients are more likely to have a higher mortality rate in areas with poorer service coverage, which they would not have experienced had they lived in an urban environment. Changes over time could be plotted and comparisons made with other areas. Unfortunately, the necessary data for such an analysis are often lacking for many of the conditions suggested for avoidable mortality analyses. Moreover, data on confounders may not be available and the resulting inferences may therefore be open to question.

A second approach is to use *health indicators*.[6] With this approach, certain sentinel conditions are assumed to reflect the general level of health care in the community, and changes in the incidence of these conditions are plotted over time and compared with data for other populations. The changes and differences that are found are then related to changes in the health service sector and are used to derive inferences about causation. However, it is difficult to know which criteria need to be met for a given condition to be acceptable as a valid health indicator. A systematic process should be followed to allow the

BOX 17.3 Healthy People 2030 Leading Health Indicators (LHIs)

LHIs by Life Stage

All Ages*

- Children, adolescents, and adults who use the oral health care system (2+ years)
- Consumption of calories from added sugars by persons aged 2 years and over (2+years)
- Drug overdose deaths
- Exposure to unhealthy air
- Homicides
- Household food insecurity and hunger
- Persons who are vaccinated annually against seasonal influenza
- Persons who know their HIV status (13+years)
- Persons with medical insurance (<65 years)
- Suicides

*Except where otherwise noted

Infants

- Infant deaths

Children and adolescents

- 4th grade students whose reading skills are at or above the proficient achievement level for their grade
- Adolescents with major depressive episodes (MDEs) who receive treatment
- Children and adolescents with obesity
- Current use of any tobacco products among adolescents

Adults and older adults

- Adults engaging in binge drinking of alcoholic beverages during the past 30 days
- Adults who meet current minimum guidelines for aerobic physical activity and muscle-strengthening activity
- Adults who receive a colorectal cancer screening based on the most recent guidelines
- Adults with hypertension whose blood pressure is under control
- Cigarette smoking in adults
- Employment among the working-age population
- Maternal deaths
- New cases of diagnosed diabetes in the population

(From Healthy People 2030. Office of Disease Prevention and Health Promotion. U.S. Department of Health & Human Services. https://health.gov/healthypeople/objectives-and-data/leading-health-indicators)

identification and implementation of a valid health indicator. Each indicator should have the following attributes: valid, reliable, relevant, realistic, measurable, well known, can be used in continuous assessment, and can effectively measure success and failure. The *beginning phase* of developing an indicator is usually through the identification of a proposed list of indicators by a group of experts in the area, followed by shortlisting the list to the indicators that fulfill most or all the attributes outlined earlier. The *next phase* includes pilot testing, which is primarily targeted to test the availability of the data and to estimate the time, effort, and finances to collect information of this indicator. The *third phase* of development is the full testing of the indicators on a larger scale and tuning the indicator based on feedback from health care personnel on the use of these indicators. The *final phase* is the full implementation of the mature indicators. At this stage, there should be a mandate for reporting the indicators and having systems in place for data collection, tabulation, analysis, and interpretation, coupled with a feedback mechanism to the intermediate and peripheral levels of the health care system.

The US Department of Health and Human Services identified 23 Leading Health Indicators (LHIs) categorized under four age groups; all ages, infants, children/adolescents, and adults/older adults. The Healthy People 2030 LHIs are presented in Box 17.3 and can be accessed on their website (https://health.gov/healthypeople). As mentioned earlier, avoidable deaths are all those defined as preventable, amenable, or both, where each death is counted only once. Where a cause of death falls within both the preventable and amenable definition, all deaths from that cause are counted in both categories when they are presented separately.

EVALUATION USING INDIVIDUAL DATA

Because of the limitations inherent in analyzing studies using grouped data (i.e., studies in which we do not have data on both health care [exposure] and health outcomes at the individual level), studies using individual data are generally preferable. If we wish to compare two populations, one receiving the care being evaluated (perhaps a new treatment) and one not

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receiving it (patients who are given "usual care"), we must ask the following two questions in order to be able to derive inferences about the effectiveness of care:

1. Are the characteristics of the two groups comparable—demographically, medically, and in terms of factors relating to prognosis?
2. Are the measurement methods comparable (e.g., diagnostic methods and the way disease is classified) in both groups?

Both issues have been discussed in earlier chapters because they also apply equally well to questions of etiology, prevention, and therapy, and they must therefore be considered in any type of study design.

An important issue in using epidemiologic approaches to study outcomes for the evaluation of health services is the need to address *prognostic stratification*. If a change in health outcome is observed after a certain type of care has been delivered, can we necessarily conclude that the change is due to the (new) health care provided, or could it be a result of differences in prognosis based on comorbidity—preexisting disease that may or may not be specifically related to the disease being studied, in severity, or in any other associated conditions that bear on prognosis? To address these issues, medical outcome studies must carry out a prognostic stratification by studying case mix and carefully characterizing the individuals studied based on disease severity.

Let us now turn to some *study designs* used in the evaluation of health services.

Randomized Designs

Randomization eliminates the problem of selection bias that results from either self-selection by the patient or selection of the patient by the health care provider. Usually, study participants are assigned to receive one type of care versus another rather than to receive care versus no care (Fig. 17.7). For many reasons, both ethical and practical, randomizing patients to receive no care usually is not considered.

Let us consider a study that used a randomized design to evaluate different approaches to health care for elderly patients who have had a stroke. Early, organized, hospital-based management has been strongly recommended for the care of patients with stroke. However, few data are available from well-conducted controlled studies to compare hospital care with specialized care at home (domiciliary care). An alternative to stroke units in the hospital is a specialized stroke team that can provide care anywhere in the hospital where stroke patients may be treated. It may not be possible for every hospital to offer care in a specialized unit to all patients who have a stroke because of space limitations and other administrative and financial issues, hence the formation of a "roaming" stroke team.

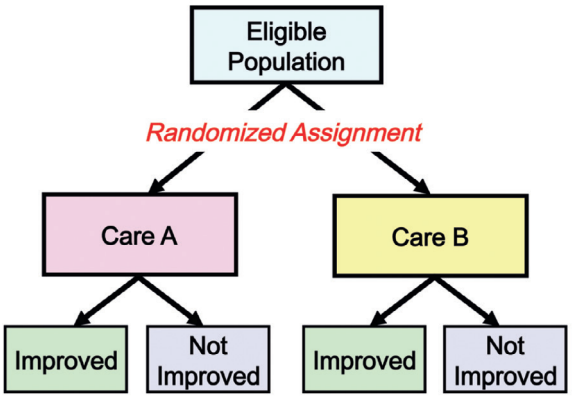

Fig. 17.7 Design of a randomized study comparing care A and care B.

To identify the optimal organizational structure for the care of patients with stroke, Kalra and colleagues[7] conducted a randomized, controlled trial to compare the efficacy of three forms of care (Fig. 17.8). Patients were randomly assigned to one of the following groups: (1) care provided in a hospital stroke unit by a stroke physician and a multidisciplinary team; (2) care provided by a multidisciplinary stroke team with expertise in stroke management; or (3) care at home (domiciliary care) provided by a specialist team. The outcome was mortality or institutionalization, which was assessed at 3, 6, and 12 months after the onset of a stroke. Data were analyzed by intention-to-treat (that is, the group they were randomized to regardless of whether it was provided). At each of the three time points, patients treated in the hospital stroke unit were less likely to die or to be institutionalized than patients in the group treated by the stroke team or the group receiving domiciliary care. Cumulative survival in the three groups is shown in Fig. 17.9. The study supports the use of specialized stroke units for the care of patients with stroke.

As seen in Fig. 17.9, an interesting and somewhat surprising finding in this study is that survival was better in patients who were randomized to receive domiciliary care (care at home) than in those randomized to receive care in the hospital by a stroke team.

A possible explanation for this observation is that patients in the domiciliary care group whose condition

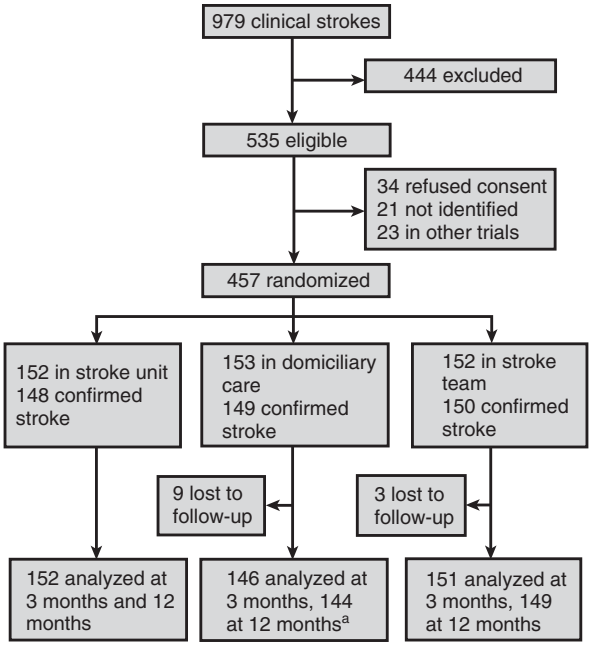

Fig. 17.8 Profile of a randomized trial of strategies for stroke care. [a]Fifty-one patients in this group were admitted to the hospital within 2 weeks of randomization, but are included in the intention-to-treat analysis. (Modified from Kalra L, Evans A, Perez I, et al. Alternative strategies for stroke care: a prospective randomized controlled trial. *Lancet*. 2000;356:894–899.)

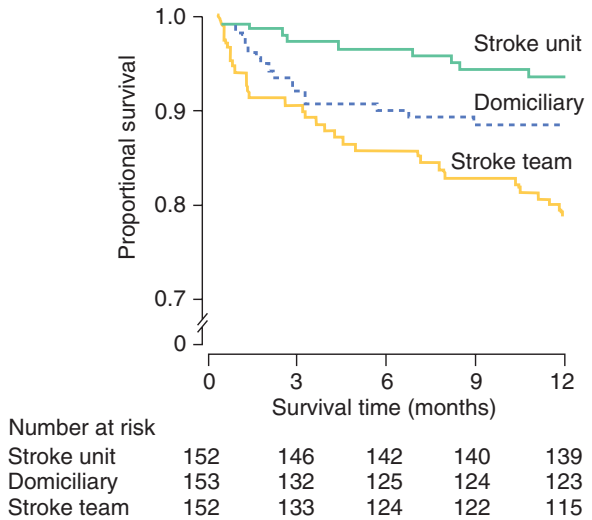

Fig. 17.9 Kaplan–Meier survival curves for different strategies of care after acute stroke. (From Kalra L, Evans A, Perez I, et al. Alternative strategies for stroke care: a prospective randomized controlled trial. *Lancet*. 2000;356:894–899.)

deteriorated or who had developed new problems were withdrawn from domiciliary care and admitted to a stroke unit. These patients were still analyzed with the domiciliary care group because an intention-to-treat analysis was used that analyzes outcome according to the original randomization. These patients may have benefited from care in the stroke unit, and if so, their outcome would tend to improve the outcome results for the domiciliary care group because of the intention-to-treat analysis.

Drummond and colleagues[8] conducted a 10-year follow-up of a randomized, controlled trial of care in a stroke rehabilitation unit. They found that management in a stroke rehabilitation unit conferred survival benefits even 10 years after the stroke. The exact reasons are not clear, but the authors suggest that one explanation may be that long-term survival is related to early reduction in disability.

Nonrandomized Designs

Many health care interventions cannot be subjected to randomized trials for several reasons. First, such trials are often logistically complex and extremely expensive. Because so many different health care measures are in use at any one time, it may not be feasible to subject all of them to randomized evaluations. Second, ethical problems may be perceived to occur in health services evaluation studies. Specifically, randomization may be viewed as an unacceptable process by many patients and by their health care providers. Third, randomized trials often take a long time to complete; because health care programs and health problems change over time, when the results of the study are finally obtained and analyzed, they may no longer be entirely relevant. For these reasons, many health care researchers look for alternative approaches that may at least yield some information. One such approach discussed earlier—*outcomes research*—generally refers to the use of data from nonrandomized studies that often use large existing data sets (or so-called "big data").

Before–After Design (Historical Controls)

If randomization is not possible or cannot be used for any reason, one possible study design to evaluate a program is to compare people who received care before a program was established (or before the health care measure became available) with those who received care from the program after it was established (or after the

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measure became available). What are the problems with the *before–after* design? First, the data obtained in each of the two periods are frequently not comparable in terms of either quality or completeness. When a new form of health service delivery is developed, evaluators of the program may want to include people who were treated in the past, before the program began, as a comparison group. The data on people treated after the new program begins may be collected using a well-designed research instrument, whereas data for past patients may include only that which may be available from health care records that had been designed and used only for clinical or administrative purposes. If we find a difference in outcome, we may not know if the observed difference is a result of the effect of the program or of differences in the quality of data from the two time periods.

Second, if we see a difference—for example, mortality is lower after a program was initiated than before the program was initiated—we do not know whether the difference is due to the program itself or to other factors that may have changed over time, such as housing, nutrition, other aspects of lifestyle, or the use of other health services.

Third, a problem of selection exists. Often, it is difficult to know whether the population studied after a program was established is actually like that seen before the program was established in terms of other factors that might affect outcome.

Does this mean that *before–after* studies have no value? No, it does not. But it does mean that such studies can only provide a suggestion—and are rarely conclusive—in demonstrating the effectiveness of a new health service.

A *before–after* design was used in a study to assess the impact of the Medicare prospective payment system (PPS) in the United States on quality of care.[9] The study was stimulated by concern that the PPS, with its closely regulated length of hospital stays and incentives for cost-cutting, might have adversely affected the quality of care. The *before–after* design was selected because the PPS was instituted nationwide, so a prospective cohort design could not be used. Data for almost 17,000 Medicare patients who were hospitalized in 1981–82 before the PPS was instituted were compared with data for patients hospitalized in 1985–86 after the PPS was in place. Quality of care was evaluated for five diseases: (1) congestive heart failure, (2) myocardial infarction, (3) pneumonia, (4) cerebrovascular accident, and (5) hip fractures. Outcome findings were adjusted for level of patient sickness on admission to the hospital. Although PPS was not found to be associated with an increase in either 30-day mortality or 6-month mortality, an increase was observed in instability at discharge (defined as the presence of conditions at discharge that clinicians agree should be corrected before discharge or monitored after discharge, and that may result in poor outcomes if not corrected).[10] The authors point out that other factors may also have changed during the time before and after institution of the PPS. Although the *before–after* design was probably the only design possible for the issue addressed in this study, the study is nevertheless susceptible to some of the problems of this type of design, which were discussed earlier.

When the change in the risk of the outcome is dramatic, the *before–after* design is akin to the so-called *natural experiment* (see Chapter 14, section titled "Approaches to Etiology in Human Populations"). It would, for example, be difficult to explain the marked decline in the rates of hospitalization for diabetes and meningitis by reasons other than the introduction of insulin and streptomycin, respectively.

Simultaneous Nonrandomized Design (Program–No Program)

One option to avoid the problems of changes that occur over calendar time is to conduct a simultaneous comparison of two populations that are not randomized, in which one population is served by the program and the other is not. This type of design is, in effect, a cohort study in which the type of health care being studied represents the "exposure." As in any cohort study, the problem arises as to how to select exposed and unexposed groups for study.

In recent years considerable interest has focused on whether higher hospital volume and higher surgeon volume relate to better patient outcomes and costs, and many studies have been carried out on these issues. An example of a simultaneous, nonrandomized study of hospital volume is one reported by Wallenstein and colleagues.[11] This study explored whether differences in patient outcomes in different hospitals related to the volume of hospital procedures performed. The authors studied hospitalizations of patients who underwent laparoscopic hysterectomy, the most common (600,000 surgeries annually) major

TABLE 17.1 Association Between Hospital Volume of Laparoscopic Hysterectomies Performed Per Year and Morbidity, Mortality, and Resource Utilization

	NUMBER OF PROCEDURES		
	<49.4/year	46.4–105/year	>105/year
Any complication (%)	5.8	5.0	4.7
Intraoperative complications (%)	2.4	2.2	2.1
Surgical site complications (%)	2.6	2.3	1.8
Medical complications (%)	1.4	1.1	1.2
Length of stay longer than 2 days (%)	10.0	7.8	5.3
Cost (dollars)	$6,527.00	$5,809.00	$5,561.00
Death (%)	0.02	0.01	0.01

Modified from Wallenstein ME, Ananth CV, Kim JH, et al. Effect of surgical volume on outcomes for laparoscopic hysterectomy for benign indications. *Obstet Gynecol*. 2012;119:709–716.

gynecologic procedure in the United States. They examined the relationship of in-hospital complications (intraoperative, surgical site, and medical) as well as length of stay and cost during the index hospitalization to the volume of surgeries performed by physicians and overall in the hospital.[11] As seen in Table 17.1, a dose-response relationship was found: the highest in-hospital complications, length of stay, and costs occurred in hospitals that had the lowest volume of hysterectomies per year. The finding that hospitals that perform more hysterectomies have lower lengths of stay and costs has important potential policy implications and argues for the regionalization of gynecologic surgical services.

It is possible that the findings relating higher hospital volumes to better patient outcomes might be due to higher volumes of procedures performed by the surgeons at these hospitals rather than to the overall volumes of procedures performed at these hospitals. Birkmeyer and colleagues addressed this issue.[12] Using Medicare claims data for 1998 and 1999, they examined mortality among all 474,108 patients who underwent one of four cardiovascular procedures or four cancer resection procedures (Fig. 17.10). They found that for most procedures the mortality rate was higher in patients operated on by low-volume surgeons than in patients operated on by high-volume surgeons. This relationship held regardless of the surgical volume of the hospital in which the surgery was performed.

Comparison of Utilizers and Nonutilizers

One approach for a simultaneous, nonrandomized study is to compare a group of people who use a health service with a group of people who do not (Fig. 17.11).

The problem of self-selection inherent in this type of design has long been recognized. Haruyama and colleagues studied the association between the personal utilization of general health checkups (GHCs) and medical expenditures (MEs) in a middle-aged Japanese population (Table 17.2).[13]

In this study, the authors recruited 33,417 residents of Soka City, Saitama Prefecture, Japan, and studied their GHC utilization from 2008 to 2010. The utilization of GHCs was divided into zero times (nonutilizers), one to three times (low-frequency utilizers), and four to six times (high-frequency utilizers). Compared with the nonutilizers, the high-frequency utilizers showed statistically significantly higher outpatient MEs. In addition, the low- and high-frequency utilizers showed statistically significantly lower inpatient MEs and total MEs than the nonutilizers. The authors concluded that outpatient MEs increased with the frequency of GHC attendance, and the early diagnosis facilitated by early outpatient consultation is more likely to lead to a slight increase in outpatient MEs but a decrease in inpatient MEs for serious diseases, resulting in a decrease in the total cost of health care.

Another example of differences between characteristics of groups under comparison is given by a study conducted by Gierisch et al. on nonadherence to breast

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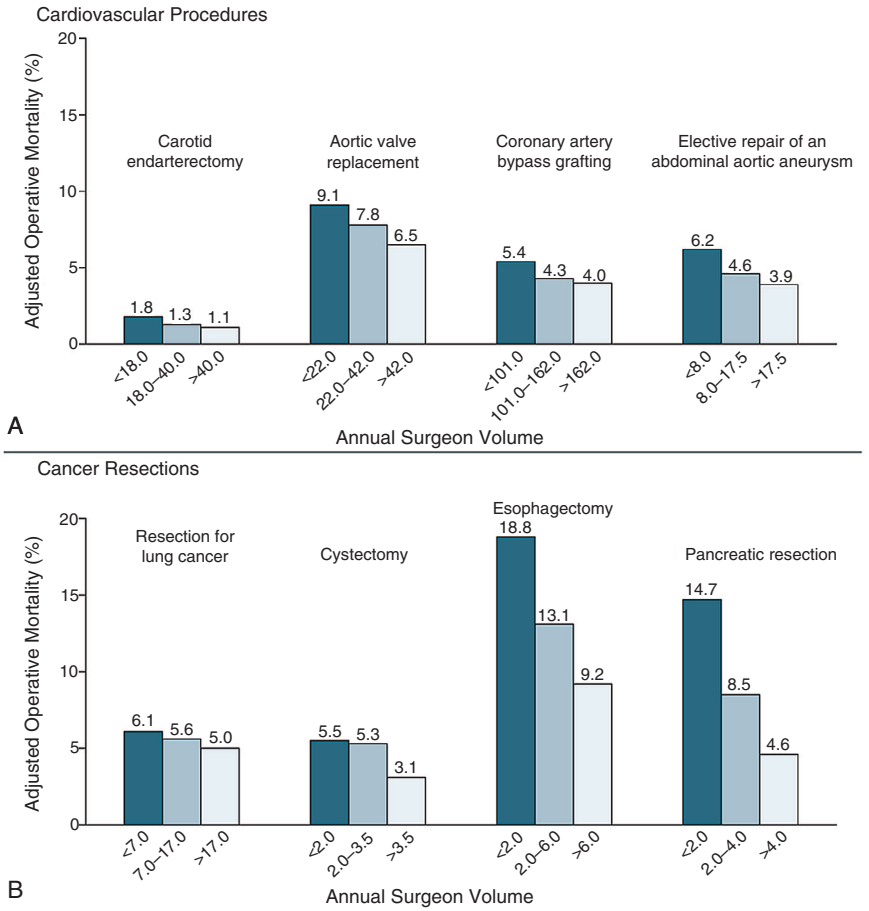

Fig. 17.10 Adjusted operative mortality among Medicare patients in 1998 and 1999 according to level of surgeon volume for four cardiovascular procedures (A) and four cancer resection procedures (B). Operative mortality was defined as the rate of death before hospital discharge or within 30 days after the index procedure. Surgeon volume was based on the total number of procedures performed. (From Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. *N Engl J Med.* 2003;349:2117–2127.)

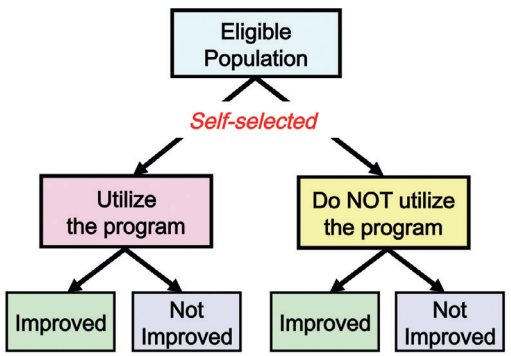

Fig. 17.11 Design of a nonrandomized cohort study comparing utilizers with nonutilizers of a program.

cancer screening with periodic mammographic examinations.[14] In this study, women who did not adhere to the screening protocol were more likely to be aged 40 to 49, and to have fair or poor self-rated health as well as difficulty in getting mammograms. As these variables are related to breast cancer (and all-cause mortality), they must be taken into consideration when using a nonrandomized design to examine the effectiveness of breast cancer screening.

Although we can try to address the selection problem by characterizing the prognostic profile of those who use care and those who do not, so long as the groups are not randomized, we are left with a gnawing uncertainty as to whether some factors were not identified in the

TABLE 17.2 Odds Ratio (and 95% Confidence Intervals) of Any Medical Consultation (Defined as Seeing a Doctor in a Period of 1 Year) According to Subgroups of General Health Checkup Utilization in Middle-Aged Japanese Population, 2010

	Nonutilizers	Low-Frequency	High-Frequency
Outpatient	1.00	2.90 (2.61–3.22)	4.37 (3.88–4.92)
Inpatient	1.00	0.79 (0.71–0.88)	0.75 (0.67–0.83)

Modified from Haruyama Y, Yamazaki T, Endo M, et al. Personal status of general health checkups and medical expenditure: a large-scale community-based retrospective cohort study. *J Epidemiol.* 2017;27(5):209–214.

study that might have differentiated utilizers and nonutilizers and, therefore, affected the health outcome.

Comparison of Eligible and Ineligible Populations

Because of the problem of possible selection biases in comparing groups of utilizers with nonutilizers, another approach compares persons who are eligible for the care being evaluated with a group of persons who are not eligible (Fig. 17.12).

The assumption being made here is that eligibility or noneligibility is not related to either prognosis or outcome; therefore, no selection bias is being introduced that might affect the inferences from the study. For example, eligibility criteria may include the type of employer or the census tract of residence. However, even with this design, one must be on the alert for factors that may introduce selection bias. For example, clearly, census tract of residence may relate to socioeconomic status. The issue of finding an appropriate noneligible population for comparison may be critical. However, ineligible persons can be selected from similar neighborhoods that could compensate for the concern with ensuring comparability of socioeconomic status. In addition, as differences between eligible and ineligible individuals may also affect external validity, on occasion adjustment for the variables that differ between these individuals improves external validity.

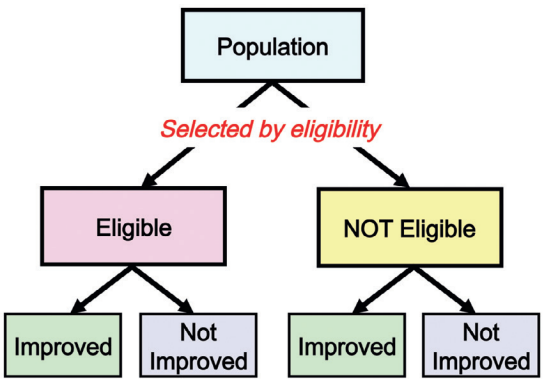

Fig. 17.12 Design of a nonrandomized cohort study comparing people eligible with people not eligible for a program.

Combination Designs

Fig. 17.13 shows a hypothetical result from a nonrandomized study comparing the morbidity level in a group that has *not* received a health service (Group X, shown in *red*) with the morbidity level in a group that *has* received the health service (Group Y, shown in *black*). Because the observed level of morbidity is lower for Group Y than for Group X, we might be tempted to conclude from these results that the health service reduces morbidity. However, as seen in Fig. 17.13 *(left of figure)*, in order to reach this conclusion, we must assume that the original levels of morbidity in the two groups were comparable at a time before the care was

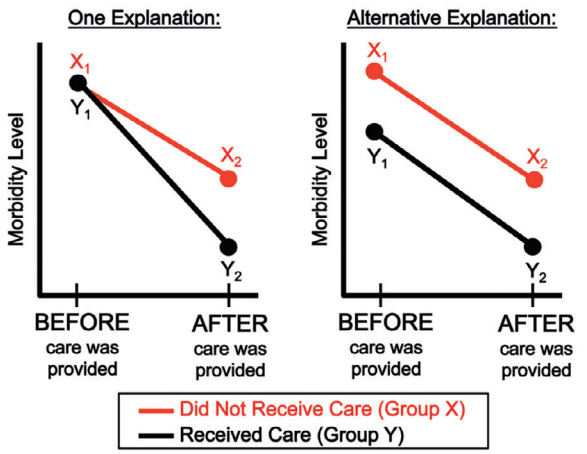

Fig. 17.13 Two possible explanations that would result in an observed difference in morbidity between Group X and Group Y after Group Y (shown in *black*) has received a health care service.

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provided to Group Y. If the morbidity levels for X_1 and Y_1 were similar, we could interpret the finding of a lower level of morbidity in Group Y (Y_2) than in Group X (X_2) at a time after which care has been administered as likely to have resulted from the care provided.

However, as seen in Fig. 17.13 *(right of figure)*, it is possible that the groups might have been originally different, and their prognoses may have differed at that time even before any care was provided. If such were the case, any differences in morbidity observed after care (i.e., Y_2 lower than X_2) might only reflect the original differences at the time before care was administered and would not necessarily shed any light on the effectiveness of the care provided. Without data on morbidity levels in the two groups before the administration of care ("baseline"), the latter explanation of the observations cannot be ruled out.

In view of this problem, another approach to program evaluation is to use a *combination design,* which combines a *before–after* design with a *program–no program* design. This approach is demonstrated in the following example, in which outpatient care for sore throats in children was evaluated.

The study is designed to assess the effectiveness of outpatient care for sore throats in children by determining whether children who are eligible for care experience lower rates of complications of untreated "strep" throat (caused by *streptococcal bacterium*), such as glomerulonephritis (inflammation of the kidney) or pediatric neuropsychiatric disorders associated with streptococcal infections (PANDAS), such as tics, than did children who are not eligible. The rationale was as follows: "strep" throats are common in children. Untreated "strep" throats can lead to complications like kidney infection. If "strep" throats are properly treated, complications can be prevented. Therefore, if these programs are effective in treating "strep" throats, fewer cases of complications should occur in children who receive the treatment.

It is possible to identify and compare subgroups of children and adolescents and to compare their rates of complications from untreated "strep." The groups could include residents of census tracts that meet eligibility criteria for comprehensive care and residents of census tracts that do not meet these eligibility criteria for comprehensive care. Both could then be compared to the city or town.

A historic example from Dr. Gordis's research[15] shows another complication of "strep" throat—rheumatic fever, which was much more common in the past century

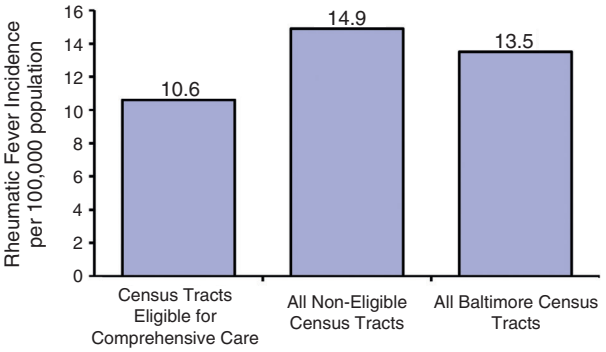

Fig. 17.14 Comprehensive care and rheumatic fever incidence per 100,000, 1968–70; Baltimore, Black population, aged 5 to 14 years. (Modified from Gordis L. Effectiveness of comprehensive-care programs in preventing rheumatic fever. *N Engl J Med.* 1973;289:331–335.)

than today. Fig. 17.14 shows a *program–no program* comparison of rheumatic fever rates in Black children in Baltimore City. In children eligible for comprehensive care based on their census tracts, the rheumatic fever rate was 10.6 per 100,000, compared with 14.9 per 100,000 in those who were not eligible. Although the rate was lower in the eligible group in this simultaneous comparison, the difference was not dramatic.

The next analysis in this combination design examined changes in rheumatic fever rates over time in both eligible and noneligible populations.

As seen in Fig. 17.15, the rheumatic fever rate declined 60% in the eligible census tracts from 1960 to 1964 (before the programs were established) to 1968–70 (after the programs were operating). In the noneligible tracts, rheumatic fever incidence was essentially unchanged (+2%). Thus, both parts of the combination design are consistent with a decline related to the care available.

However, because many changes had occurred in Baltimore City during this time, it was not certain whether the care provided by the programs was indeed responsible for the decline in rheumatic fever. Another analysis was therefore carried out. In children, streptococcal throat infection can be either symptomatic or asymptomatic. Clearly, only a child with a symptomatic sore throat would have been brought to a clinic. If we hypothesize that the care in the clinic was responsible for the reduction in rheumatic fever incidence, we expect the decline in incidence to be limited to children with symptomatic clinical sore throats who would have

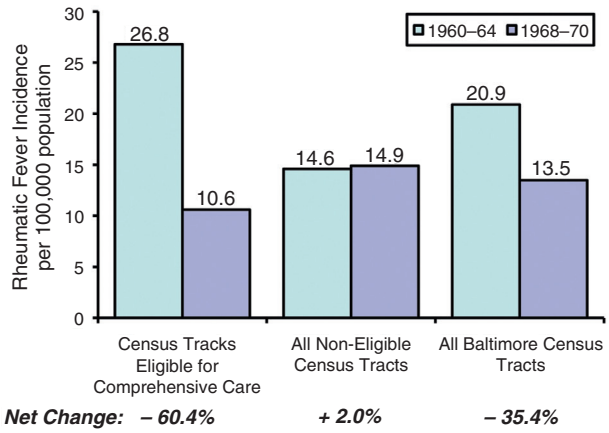

Fig. 17.15 Comprehensive care and changes in rheumatic fever incidence per 100,000, 1960–64 and 1968–70; Baltimore, Black population, aged 5 to 14 years. (Modified from Gordis L. Effectiveness of comprehensive-care programs in preventing rheumatic fever. *N Engl J Med.* 1973;289:331–335.)

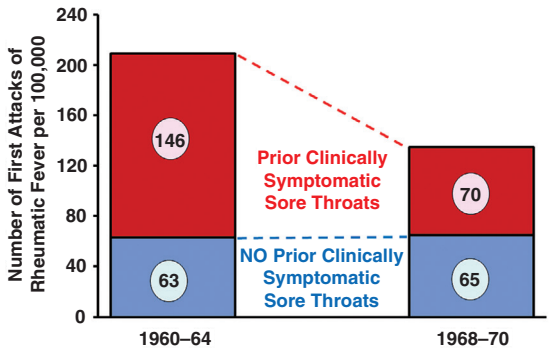

Fig. 17.16 Changes in the annual incidence of first attacks of rheumatic fever in relation to the presence or absence of preceding clinically symptomatic sore throat. As seen in the figure, the entire decline in first attacks of rheumatic fever was due to a decline in first attacks of rheumatic fever that were preceded by clinically symptomatic sore throats. (Modified from Gordis L. Effectiveness of comprehensive-care programs in preventing rheumatic fever. *N Engl J Med.* 1973;289:331–335.)

sought care, and not to have occurred in asymptomatic children who had no clinically apparent infections.

As seen in Fig. 17.16, the entire decline was limited to children with prior clinically overt infection; no change in rheumatic fever incidence occurred in those children with asymptomatic "strep" throat. These findings are therefore highly consistent with the suggestion that it was the medical care, or some factor closely associated with it, which was responsible for the decline in rheumatic fever incidence.

Case-Control Studies

The use of the case-control design for evaluating health services, including vaccines and other forms of prevention and screening programs, has elicited increasing interest in the field of public health. Although the case-control design has been applied primarily to exploratory etiologic studies, when appropriate data are obtainable, this design can serve as a useful, but limited, surrogate for randomized trials. However, because this design requires definition and specification of cases, it is most applicable to studies of *prevention* of specific diseases. The "exposure" is then the specific preventive or other health measure that is being assessed. As in most health services research, stratification by disease severity and by other possible prognostic factors is essential for appropriate interpretation of the findings. The methodologic problems associated with such studies (which are discussed extensively in Chapter 7) also arise when the case-control design is used for evaluating effectiveness. In particular, these studies need to address the selection of controls and issues associated with confounders.

CONCLUSION

This chapter has reviewed the application of basic epidemiologic study designs to the evaluation of health services. Many of the issues that arise are like those that arise in etiologic studies, although at times they present a different twist. In etiologic studies, we are primarily interested in the possible association of a potential causal factor and a specific disease, and factors such as health services accessibility often represent possible confounders that must be taken into account. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), evaluation of determinants of atrial fibrillation must consider the potential confounding effect of health insurance status (a marker of access to health care), as diagnosis of this condition is often made during a patient's encounter with a physician.[16]

In health care evaluation studies, we are primarily interested in possible associations of a health care or preventive activity and a particular disease outcome, and factors such as preexisting disease and other prognostic and risk factors become potential confounders that must be taken into consideration. Consequently, although

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many of the same design issues remain, the focus in evaluation research is often on different issues of measurement and assessment. The randomized trial remains the optimal method for demonstrating the effectiveness of a health intervention. However, ethical issues may remain in play, as it may be unethical to withhold a known or effective treatment in a randomized trial design. In initiating any evaluation study of health care, we should ask at the outset whether it is biologically and clinically plausible, given our current knowledge, to expect a specific benefit from the care being evaluated.

For practical reasons, nonrandomized observations are also necessary and must be capitalized in the attempt to expand our efforts at health services evaluation. Critics of randomized trials have pointed out that such studies have included—and can only include—a small fraction of all patients receiving care in the health care system so that generalizability (external validity) of the results is a potential problem. Although this is true, generalizability is a problem with any study, no matter how large the study population. Nevertheless, even as we further refine the methodology of clinical trials, we also need improved methods to enhance the information that can be obtained from nonrandomized evaluations of health services.

The study of specific components of care, rather than a care program per se, is essential. In this way, if an effective element can be identified in a mix of many modalities, the others can be eliminated, and the quality of care can be enhanced in a cost-effective fashion.

In Chapter 18, the discussion of evaluation is extended to a specific type of health services program: screening (early detection) for disease in human populations.

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REVIEW QUESTIONS FOR CHAPTER 17

1. *All of the following are measures of process of health care in a clinic except:*
   - **a.** Proportion of patients in whom blood pressure is measured
   - **b.** Proportion of patients who have complications of a disease
   - **c.** Proportion of patients advised to stop smoking
   - **d.** Proportion of patients whose height and weight are measured
   - **e.** Proportion of patients whose bill is reduced because of financial need
2. *The extent to which a specific health care treatment, service, procedure, program, or other intervention does what it is intended to do when used in a community-dwelling population is termed its:*
   - **a.** Efficacy
   - **b.** Effectiveness
   - **c.** Effect modification
   - **d.** Efficiency
   - **e.** None of the above
3. *The extent to which a specific health care treatment, service, procedure, program, or other intervention produces a beneficial result under ideal controlled conditions is its:*
   - **a.** Efficacy
   - **b.** Effectiveness
   - **c.** Effect modification
   - **d.** Efficiency
   - **e.** None of the above
4. *A major problem in using a historical control design for evaluating a health service using case-fatality (CF) as an outcome is that if the CF is lower after provision of the health service was started, then:*
   - **a.** The lower CF could be caused by changing prevalence of the disease
   - **b.** The lower CF may be a result of decreasing incidence
   - **c.** The lower CF may be an indirect effect of the new health service
   - **d.** The CF may have been affected by changes in factors that are not related to the new health service
   - **e.** None of the above

Question 5 is based on the information given below:

In-Hospital Case-Fatality (CF) for 100 Men Not Treated in a Coronary Care Unit (CCU) and for 100 Men Treated in a CCU, According to Three Clinical Grades of Severity of Myocardial Infarction (MI)

	NON-CCU (NO. OF PATIENTS)			CCU (NO. OF PATIENTS)		
Clinical Grade	Total	Died	CF (%)	Total	Died	CF (%)
Mild	60	12	20	10	3	30
Severe	36	18	50	60	18	30
Shock	4	4	100	30	13	43

The results shown are based on a comparison of the last 100 patients treated before the CCU was installed and the first 100 patients treated within the CCU. All 200 patients were admitted during the same month.

You may assume that this is the *only hospital* in the town and that the natural history of MI was *unchanged* during this period.

5. *The authors concluded that the CCU was very beneficial for men with severe MI and for those in shock, because the in-hospital CFs for these categories were much lower in the CCU. This conclusion:*
   - **a.** Is correct
   - **b.** May be incorrect because CFs were used rather than mortality rates
   - **c.** May be incorrect because of a referral bias of patients to this hospital from hospitals in distant towns
   - **d.** May be incorrect because of differences in the assignment of the clinical severity grade before and after the opening of the CCU
   - **e.** May be incorrect because of failure to recognize a possible decrease in the annual incidence rate of MI in recent years

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18

Epidemiologic Approach to Evaluating Screening Programs

For all sad words of tongue or pen
The saddest are these:
"it might have been."[1]

—J.G. Whittier, 1856

If, of all words of tongue and pen,
The saddest are, "It might have been,"
More sad are these we daily see:
"It is, but hadn't ought to be."[2]

—Bret Harte, 1871

LEARNING OBJECTIVES

- To extend the discussion of the validity and reliability of screening tests introduced in Chapter 5.
- To revisit the natural history of disease and introduce the concepts of lead time and critical point.
- To describe the major sources of bias that must be considered in assessing study findings that compare screened and unscreened populations, including referral bias, length-biased sampling, lead time bias, 5-year survival, and overdiagnosis bias.
- To discuss various study designs for evaluating screening programs, including nonrandomized and randomized studies and the challenges of interpreting the results of these studies.
- To discuss problems in assessing the sensitivity and specificity of commercially developed screening tests.
- To introduce issues associated with cost-benefit analyses of screening.

In Chapter 1, we distinguished among primary, secondary, and tertiary prevention. In Section II, we discussed the design and interpretation of studies that aim to identify risk factors or etiologic factors for disease so that the occurrence of disease can be completely prevented—*primary prevention.* In this chapter, we address how epidemiology is used to evaluate the effectiveness of screening programs for the early detection of disease—*secondary prevention.* This subject is particularly important in both public health and clinical practice because there is increasing acceptance of a physician's obligation to include prevention along with diagnosis and treatment as major responsibilities in the clinical care of patients.

The validity and reliability of screening tests were discussed in Chapter 5. In this chapter, we will discuss some of the methodologic issues that must be considered in deriving inferences about the benefits that may come to those who undergo screening tests.

The question of whether patients benefit from the early detection of disease includes the following components:

1. Can the disease be detected early?
2. What are the sensitivity and the specificity of the test?
3. What is the predictive value of the test?
4. How serious is the problem of false-positive test results?
5. What is the cost of early detection in terms of funds, resources, and emotional impact?

6. Can the subject be harmed by having a screening test?
7. Do the individuals in whom disease is detected early benefit from the early detection, and is there an overall benefit to those who are screened?

In this chapter, we primarily address the last question. Several of the other issues in the preceding list are considered only in the context of this question.

The term *early detection of disease* means diagnosing a disease at an earlier stage than would usually occur in standard clinical practice. This usually denotes detecting disease at a presymptomatic stage, at which point the patient has no clinical complaint (no symptoms or signs) and therefore no reason to seek medical care for the condition. The assumption in screening is that an appropriate intervention is available for the disease that is detected and that the medical intervention can be more effectively applied if the disease is detected at an earlier stage.

At first glance, the question of whether people benefit from early detection of disease may seem somewhat surprising. In some instances, it may be pragmatic to only screen those who are at high risk of developing the disease of interest. Intuitively, it would seem obvious that early detection is beneficial and that intervention at an earlier stage of the disease process is more effective and/or easier to implement than a later intervention. In effect, these assumptions represent a "surgical" view; for example, every malignant lesion is localized at some early stage, and at this stage it can be successfully excised before regional spread occurs or certainly before widespread metastases develop. However, the intuitive attractiveness of such a concept should not blind us to the fact that throughout the history of medicine, deeply felt convictions have often turned out to be erroneous when they were not supported by data obtained from appropriately designed and rigorously conducted studies. Consequently, regardless of the attractiveness of the idea of the beneficial aspects of early disease detection, both to clinicians involved in prevention and therapy and to those involved in community-based prevention programs, the evidence to support the validity of this concept must be rigorously examined.

As in evaluating any type of health service, screening can be evaluated using process or outcome measures. Box 18.1 provides a list of examples of operational measures that includes process measures, as well as measurements of yield and information produced by the screening program.

We are particularly interested in the question of what benefit is gained by people who undergo screening in a screening program. However, just as is the case with evaluation of health services (discussed in Chapter 17), there is little advantage to improving the *process* of screening if persons who are screened derive no benefit. That is, if early detection does not lead to any improvement in survival, what is the gain to patients to be detected earlier? Perhaps just a longer remaining time to worry with poor quality of life! We will therefore examine some of the problems associated with determining whether early detection of disease confers benefits to the individual who undergoes screening (in other words, whether the outcome is improved by screening).

What do we mean by *outcome?* To answer the question of whether patients benefit, we must precisely define what we mean by benefit, whether this benefit is meaningful to the patient or family, and what outcome or outcomes are considered to be evidence of patient benefit. Some of the possible outcome measures that might be used are shown in Box 18.2.

BOX 18.1 Assessing the Effectiveness of Screening Programs Using Operational Measures

1. Number of people screened
2. Proportion of target populations screened and number of times screened
3. Detected prevalence of preclinical disease
4. Total costs of the program
5. Costs per case found
6. Costs per previously unknown case found
7. Proportion of positive screenees brought to final diagnosis and treatment
8. Predictive value of a positive test in population screened

(Modified from Hulka BS. Degrees of proof and practical application. *Cancer.* 1988;62:1776–1780. Copyright © 1988 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

BOX 18.2 Assessing the Effectiveness of Screening Programs Using Outcome Measures

1. Reduction of mortality in the population screened
2. Reduction of case-fatality in screened individuals
3. Increase in percent of cases detected at earlier stages
4. Reduction in complications
5. Prevention of or reduction in recurrences or metastases
6. Improvement of quality of life in screened individuals

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NATURAL HISTORY OF DISEASE

To discuss the methodologic issues involved in evaluating the benefits of screening, let us examine in further detail the natural history of disease (first discussed in Chapter 6).

We will begin by placing screening in its appropriate place on the timeline of the natural history of disease and will do so in relation to the different approaches to prevention discussed in Chapter 1.

Fig. 18.1A is a schematic representation of the natural history of a disease in an individual. At some point, biologic onset of disease occurs. This may be a subcellular change, such as an alteration in DNA or programmed cell death (*apoptosis*), which at this point is generally undetectable. At some later point the disease becomes symptomatic, or clinical signs develop (i.e., the disease now moves into a clinical phase). The clinical signs and symptoms (e.g., blood in the stool) prompt the patient to seek care, after which a diagnosis is made and appropriate therapy is instituted, the ultimate outcome of which may be cure, control of the disease, prevention or delay of incident complications, disability, or death.

As seen in Fig. 18.1B, the onset of symptoms marks an important point in the natural history of a disease. The period when disease is present can be divided into two phases. The period from biologic onset of the disease to the development of signs and symptoms is called the *preclinical phase* of the disease, which comes before the *clinical phase* of the disease.

The period from the time when signs and symptoms develop to an ultimate outcome such as possible cure, control of the disease, or death is referred to as the *clinical phase* of the disease. As seen in Fig. 18.1C and D, *primary prevention* (i.e., preventing the development of disease by preventing or reducing exposure to disease-causing agents) denotes an intervention before a disease has developed. (Prevention of risk factor exposure, such as immunization and prevention of smoking initiation, is also known as *primordial prevention*.) *Secondary*

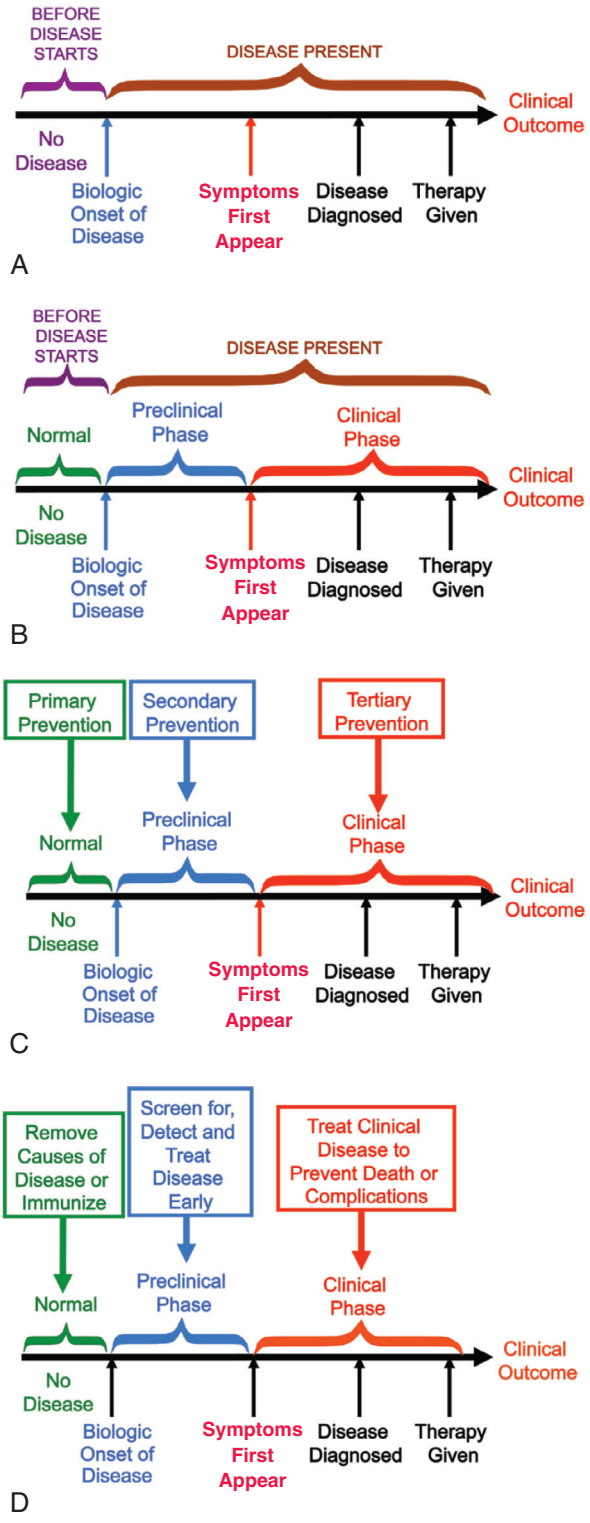

Fig. 18.1 **(A)** Natural history of a disease. **(B)** Natural history of a disease with preclinical and clinical phases. **(C)** Natural history of a disease with points for primary, secondary, and tertiary prevention. **(D)** Natural history of a disease with specific primary, secondary, and tertiary prevention measures.

prevention, detecting disease at an earlier stage than usual, such as by screening, takes place during the *preclinical phase* of an illness (i.e., after the disease has developed but before clinical signs and symptoms have appeared). *Tertiary prevention* refers to treating clinically ill individuals to prevent complications of the illness (e.g., stroke rehabilitation), including death of the patient.

If we want to detect disease earlier than usual through programs of health education, we could encourage symptomatic persons to seek medical care sooner. However, a major challenge lies in identifying persons with disease who do not have any symptoms. Our focus in this chapter is on identifying disease in persons who have not yet developed symptoms and who are in the preclinical phase of illness.

Let us now take a closer look at the *preclinical phase* of the disease (Fig. 18.2). At some point during the preclinical phase, it becomes possible to detect the disease by using currently available tests (see Fig. 18.2A). The interval from this point to the development of signs and symptoms is the *detectable preclinical phase* of the disease (see Fig. 18.2B). When disease is detected by a screening test, the time of diagnosis is advanced to an earlier point in the natural history of the disease than would have happened if the screening was not done. The *lead time* is defined as the interval by which the time of diagnosis is advanced by screening for the early detection of disease compared with the usual time of diagnosis (see Fig. 18.2C). The concept of lead time is inherent in the idea of screening and then detecting a disease earlier than it would usually be found.

Another important concept in screening is if there is a *critical point* in the natural history of a disease (Fig. 18.3A).[3] This is a point in the natural history before which treatment is more effective and/or less difficult to administer. If a disease is potentially curable, cure may be possible before this point but not later. For example, in a patient with breast cancer, one critical point would be that at which the disease spreads from the breast to the axillary lymph nodes. If the disease is detected and treated prior to spreading, the prognosis is much better than after spread to the nodes has taken place.

As shown in Fig. 18.3B, there may be multiple critical points in the natural history of a disease. For example, in the patient with breast cancer, a second critical point may be that at which disease spreads from the axillary

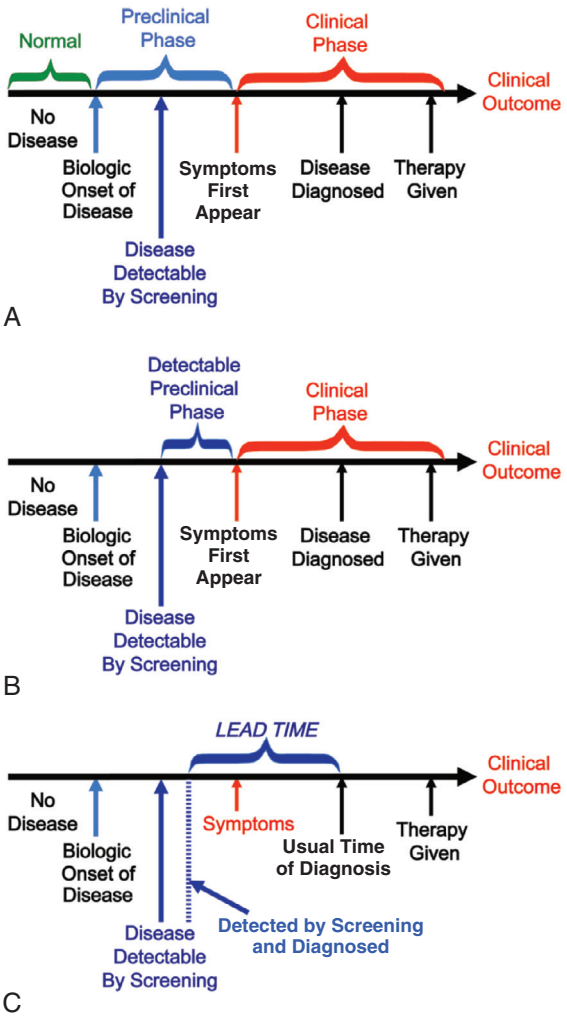

Fig. 18.2 Preclinical phase of the disease. **(A)** Natural history with point at which disease is detectable by screening. **(B)** Natural history with detectable preclinical phase. **(C)** Natural history with lead time.

nodes to other more distant parts of the body. Prognosis is still better when the disease is confined to the axillary lymph nodes than when systemic spread has occurred, but not as good as when the disease is confined to the breast. The concept of multiple critical points suggests that the earlier the diagnosis, the better the prognosis.

However, the critical point is somewhat theoretical because we usually cannot identify when the critical point is reached. However, it is a very important concept in screening. If we cannot envision one or more critical points in the natural history of a disease, there is clearly

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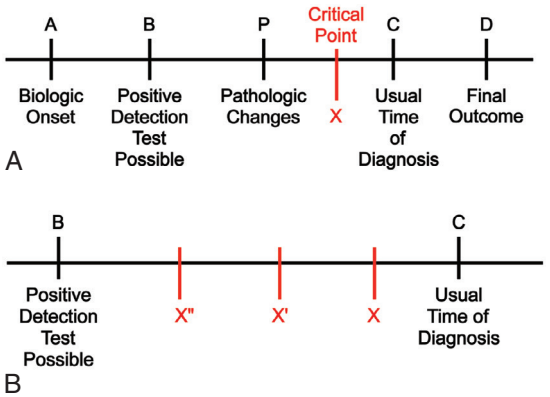

Fig. 18.3 **(A)** A single critical point in the natural history of a disease. **(B)** Multiple critical points in the natural history of a disease. (Modified from Hutchison GB. Evaluation of preventive services. *J Chronic Dis*. 1960;11:497–508.)

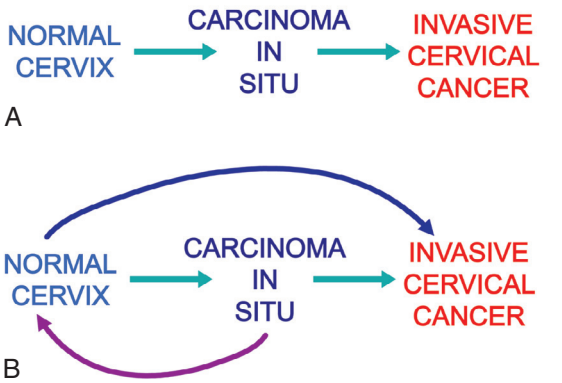

Fig. 18.4 **(A)** Natural history of cervical cancer: I. Progression from normal cervix to invasive cancer. **(B)** Natural history of cervical cancer: II. Extremely rapid progression and spontaneous regression.

no rationale for screening and early detection. Early detection presumes that a biologic point exists in the natural history of a disease before which treatment will benefit a person more than if they are treated after that point.

PATTERN OF DISEASE PROGRESSION

We might expect to see a potential benefit from screening and early detection if the following two assumptions hold:

1. All or most clinical cases of a disease first go through a detectable preclinical phase.
2. In the absence of intervention, all or most cases in a preclinical phase progress to a clinical phase.

Both assumptions are reasonably self-evident. For example, if none of the preclinical cases progress to clinical cases, there is no reason to perform screening tests. Alternatively, if none of the clinical cases passes through a preclinical phase, there is no reason to perform screening tests. Thus, both assumptions are important in assessing any potential benefit from screening.

Let us look at the example of screening for cervical cancer. It has been some 80 years since the Papanicolaou (Pap) smear was developed to test for the presence of precancerous or cancerous cells of the cervix, the opening of the uterus. During this routine procedure, cervical cells are scraped from around the cervix and then examined. The biology of cervical cancer has been well documented, going through a series of steps from dysplasia to carcinoma in situ, to invasive cervical cancer that often takes years to develop. Early detection often allows treatment to stop the progression of this cancer. More recently, with the documentation of the viral origins of cervical cancer (human papillomavirus [HPV] infection), cervical cancer screening is now done by HPV detection with less frequent Pap tests. Fig. 18.4A shows the progression from a normal cervix to cervical cancer. We might expect that detection and treatment of more cases at the in situ (noninvasive) stage would be reflected in a commensurate reduction in the number of cases that progress to invasive disease.

However, the two assumptions associated with early detection are open to question. In certain situations, and unlike what happens in cervical cancer, the preclinical phase may be so short that the disease is unlikely to be detected by any periodic screening program. In addition, there is increasing evidence that spontaneous regression may occur in some diseases; therefore, not every preclinical case inexorably progresses to clinical disease. Exposures may also regress; importantly, this is the case with HPV detection in women—most of the HPV types detected in routine screening will generally revert (spontaneously disappear) in the following 6 months!

However, evaluating the benefits of cervical cancer screening is complicated by the problem that some cases progress through the in situ stage so rapidly and the preclinical stage is so brief, that for all practical purposes there is no detectable preclinical stage during

which disease can be identified by screening. In addition, nuclear DNA quantitation studies suggest that cervical intraepithelial abnormalities may exist either as a reversible state or as an irreversible precursor of invasive cancer. Data also suggest that some cases of cervical intraepithelial neoplasia detected by a Pap smear regress spontaneously, particularly in the earlier stages, but also in the later stage (carcinoma in situ). In one study, one-third of women with abnormal Pap smears who refused any intervention were later found to have normal Pap smears. In addition, data suggest that most, if not all, in situ cervical cancers are associated with different types of papillomaviruses. Only these types of early non-invasive cancers associated with certain high-risk types of papillomavirus progress to invasive cancer, so we may be dealing with heterogeneity of both the causal agent and disease.

The simple model of progression from normal cervix to invasive cervical cancer seen in Fig. 18.4A would suggest that early detection followed by effective intervention would be reflected by a commensurate reduction in the number of invasive lesions that subsequently develop. A more accurate presentation of the natural history of cervical cancer may be that seen in Fig. 18.4B. The extent of both phenomena, spontaneous regression and extremely rapid progression, clearly influences the size of the decrease in invasive disease that might be expected to result from early detection and intervention and must therefore be taken into account in assessing the benefits of screening. Although these issues have been demonstrated for cervical cancer, they are clearly relevant to evaluating the benefits of screening for many diseases.

METHODOLOGIC ISSUES

To interpret the findings in a study designed to evaluate the benefits of screening, certain methodologic problems must be taken into account. Most studies of screening programs that have been reported are not randomized trials because of the difficulties of randomizing a population for screening. The question is, therefore, can we examine a group of people who have been screened and compare their mortality to a group of people who have not been screened (i.e., use a cohort design, which is observational, to evaluate the effectiveness of screening)?

Let us assume that we can compare a population of people who have been screened for a disease with a population of people who have not been screened for the disease. Let us assume further that a viable and effective treatment is available and will be used effectively for those in whom disease is detected. If we find a lower mortality from the disease in those in whom disease was identified through screening than in those in whom disease was not detected in this manner, can we conclude that screening and early detection of disease have been beneficial? Let us turn to some of the methodologic issues involved.

Selection Biases

Referral Bias (Volunteer Bias)

In coming to a conclusion about the benefits of screening, the first question we might ask is whether there was a selection bias in terms of who was screened and who was not. We would like to be able to assume that those who were screened had the same characteristics as those who were not screened (i.e., they were similar to one another in all ways except their screening history). However, there are many differences in the characteristics of those who participate in screening or take advantage of other health programs and those who do not. Many studies have shown volunteers to be healthier than the general population and to be more likely to comply (to be adherent) with medical recommendations. If, for example, persons whose disease had a better prognosis from the outset were either referred for screening or were self-selected, we might observe lower mortality in the screened group even if early detection played no role in improving prognosis. Of course, it is also possible that volunteers may include many people who are at high risk and who volunteer for screening because they have anxieties based on a positive family history or their own lifestyle characteristics. The problem is that we do not know in which direction the selection bias might operate and how it might affect the study results.

The problem of selection bias that most significantly affects our interpretation of the findings is best addressed by carrying out the comparison with a randomized study in which care is taken that the two groups have comparable initial prognostic profiles (Fig. 18.5).

Length-Biased Sampling (Prognostic Selection)

The second type of problem that arises in interpreting the results of a comparison of a screened and an unscreened

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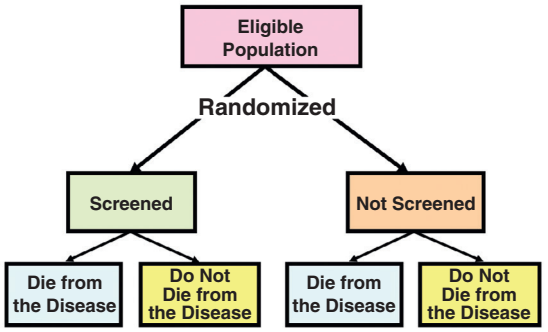

Fig. 18.5 Design of a randomized trial of the benefits of screening.

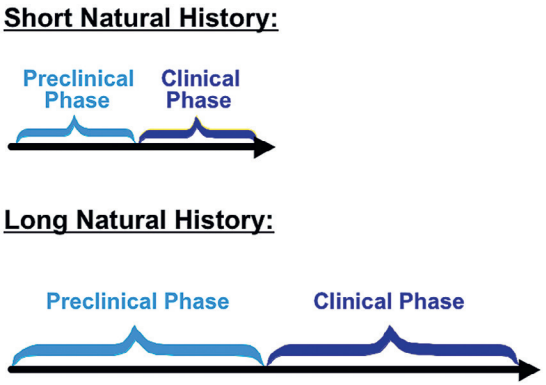

Fig. 18.6 Short and long natural histories of disease: relationship of length of clinical phase to length of preclinical phase.

group is a possible selection bias; this does not relate to who comes for screening but rather to the type of disease that is detected by the screening. The question is: Does screening selectively identify cases of the disease which have a better prognosis? In other words, do the cases found through screening have a better natural history regardless of how early therapy is initiated? If the outcome of those in whom disease is detected by screening is found to be better than the outcome of those who were not screened, and in whom disease was identified during the usual course of clinical care, could the better outcome among those who are screened result from selective identification by screening of persons with a better prognosis? Could the better outcome be unrelated to the time of diagnostic and treatment interventions?

How could this come about? Recall the natural history of disease, with clinical and preclinical phases, as shown in Fig. 18.1B. We know that the clinical phase of illness differs in length for different people (i.e., there is a natural distribution of clinical illness parameters in every population). For example, some patients with colon cancer die soon after diagnosis, whereas others survive for many years. What appears to be the same disease may include individuals with different lengths of a clinical phase. Another example is patients who develop COVID-19 and also have certain comorbidities get sicker and experience the symptoms for relatively longer duration than those who are otherwise healthy.

What about the preclinical phase in these individuals? Actually, each patient's disease has a single continuous natural history, which we divide into preclinical and clinical phases (Fig. 18.6) on the basis of the point in time at which signs and symptoms develop. In some, the natural history is brief, and in others the natural history is protracted. This suggests that if a person has a slowly progressive natural history with a long clinical phase, the preclinical phase will also be long. In contrast, if a person has a rapidly progressive disease process and a short natural history, the clinical phase is likely to be short, and it seems reasonable to conclude that the preclinical phase will also be short. There are in fact data to support the notion that a long clinical phase is associated with a long preclinical phase and a short clinical phase is associated with a short preclinical phase. Lung cancer serves as an example: it has a short clinical phase and most likely also a short preclinical phase, as suggested by the inconsistent results from clinical trials of smokers screened by computed tomography, with some trials showing an approximately 15% to 20% effectiveness and others showing no effectiveness whatsoever.[4]

Remember that our purpose in screening is to detect the disease during the preclinical phase because during the clinical phase the patient is already aware of the problem and even without screening will probably seek medical care for symptoms. If we mount a one-time screening program in a community, which group of patients are we likely to identify—those with a short preclinical phase or those with a long preclinical phase?

To answer this question, let us consider a small population that is screened for a certain disease (Fig. 18.7). As shown in Fig. 18.7, each case has a preclinical and a clinical phase. The figure is drawn so that each preclinical phase is the same length as its associated clinical phase. Patients in the clinical phase will be identified in the usual course of medical care, so the purpose of the screening is to identify cases in the preclinical state (i.e.,

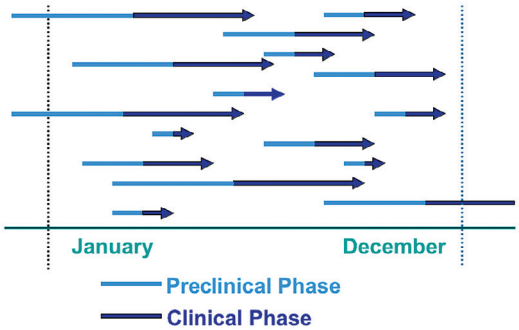

Fig. 18.7 Hypothetical population of individuals with long and short natural histories.

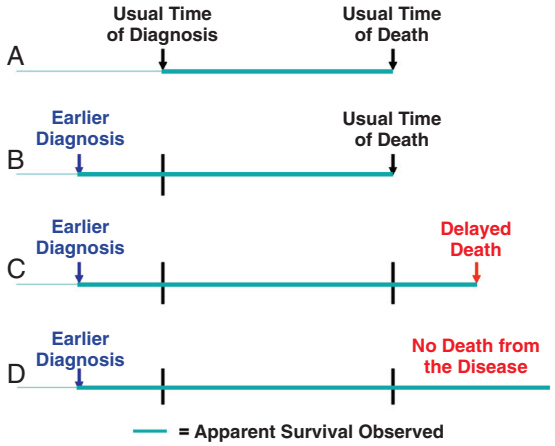

Fig. 18.8 **(A)** Outcome of diagnosis at the usual time, without screening. **(B–D)** Three possible outcomes of an earlier diagnosis as a result of a screening program.

before any onset of signs or symptoms). Note that the lengths of the preclinical phases of cases represented here vary. The longer the preclinical phase, the more likely the screening program will detect the case while it is still preclinical. For example, if we screen once a year for a disease for which the preclinical phase is only 24 hours long, we will clearly miss virtually all of the cases during the preclinical phase. However, if the preclinical phase is 1 year long, many more cases will be identified during that time. Screening tends to selectively identify those cases that have longer preclinical phases of illness. Consequently, even if the subsequent therapy had no effect, screening would still selectively identify persons with a long preclinical phase, and they would consequently experience a longer clinical phase (i.e., those with a better prognosis). These people would have a better prognosis even if there were no screening program or even if there were no true benefits from screening.

This problem can be addressed in several ways. One approach is to use an experimental randomized design in which care is taken to keep the groups comparable in terms of the lengths of the detectable preclinical phase of illness. However, this may not be easy. In addition, survival would have to be examined for all members of each group (i.e., the screened and unscreened). In the screened group, survival would be calculated for those in whom disease is detected by screening and for those in whom disease is detected between screening examinations, the so-called *interval cases.* We will return to the importance of interval cases later in this chapter.

Lead Time Bias

Another problem that arises in comparing survival in people who are screened with survival in those who are not screened is *lead time bias* (first illustrated in Fig. 18.2C)—how much earlier can the diagnosis be made if the disease is detected by screening compared with the usual timing of the diagnosis if screening were not carried out?

Consider four individuals with a certain disease shown by the four timelines in Fig. 18.8. The thicker part of each horizontal line denotes the apparent survival that is observed. The first timeline (A) shows the usual time of diagnosis and the usual time of death. The second timeline (B) shows an earlier time of diagnosis but the same time of death. Survival *seems* better because the interval from diagnosis to death is longer, but the patient is not any better off because death has not been delayed. The third timeline (C) shows earlier diagnosis and a delay in death from the disease—clearly a benefit to the patient (assuming that subsequent quality of life is good). Finally, the fourth timeline (D) shows earlier diagnosis, with subsequent prevention of death from the disease.

The benefits we seek in screening are delay or prevention of death. Although we have chosen to focus on mortality in this chapter, we could also have used morbidity parameters, recurrence, quality of life, or patient satisfaction as valid measures of outcome.

Lead Time and 5-Year Survival

Five-year survival is a frequently used measure of therapeutic success, particularly in patients with cancer following different therapeutic and management strategies.

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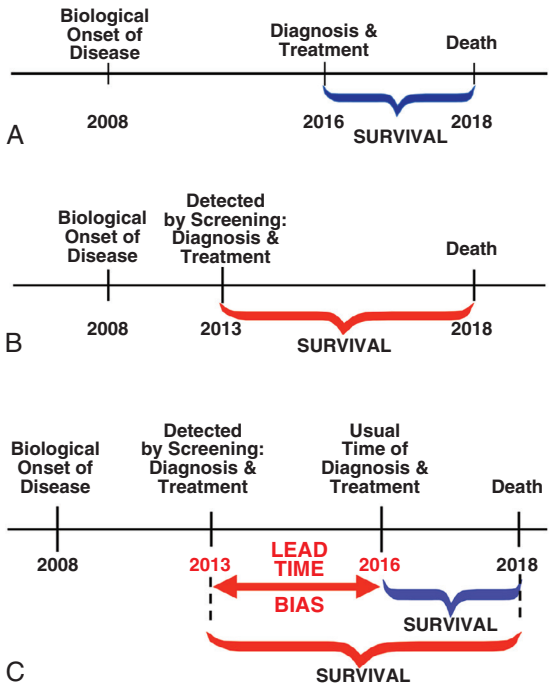

Fig. 18.9 **(A)** Natural history of a patient with colon cancer without screening. Disease diagnosed and treated in 2008. **(B)** Disease detected by screening 3 years earlier in 2013 (lead time). **(C)** Lead time bias resulting from screening 3 years earlier.

Let us examine the possible effect of lead time on apparent 5-year survival.

Fig. 18.9A shows the natural history of disease in a hypothetical patient with colon cancer, which was diagnosed in the usual clinical context without any screening. Biologic onset of the disease was in 2008. The patient became aware of symptoms in 2016 and had a diagnostic workup leading to a diagnosis of colon cancer. Surgery was performed in 2016, but the patient died of colon cancer in 2018. This patient has survived for 2 years (2016–18) and clearly is not a 5-year survivor. If we use 5-year survival as an index of treatment success, this patient is a treatment failure.

Consider what might happen to this patient if he resides in a community in which a screening program is initiated (see Fig. 18.9B). For this hypothetical example only, let us assume that there is actually no benefit from early detection (i.e., the natural history of colon cancer is unaffected by early intervention). In this case the patient is asymptomatic but undergoes a routine screening test in 2013, the result of which is positive. In 2013, surgery is performed, but the patient dies in 2018. The patient has survived 5 years and is now clearly a 5-year survivor. However, he is a 5-year survivor not because death has been delayed but because the diagnosis has been made earlier. When we compare this screening scenario with the scenario without screening (see Fig. 18.9A), it is apparent the patient has not derived any benefit from earlier detection in terms of having lived any longer. Indeed, the patient may have lost out in terms of quality of life because the earlier detection of disease by screening gave him an additional 3 years of postoperative and other medical care and may have deprived him of 3 years of normal life. This problem of an *illusion* of better survival only because of earlier detection is called the *lead time bias*, as shown in Fig. 18.9C.

Thus, even if there is no true benefit from early detection of a disease, there will *appear* to be a benefit associated with screening, even if death is not delayed, because of an earlier point of diagnosis from which survival is measured. This is not to say that early detection carries no benefit; rather, even without any benefit, the lead time associated with early detection suggests the appearance of a benefit in the form of enhanced survival. Lead time must therefore be taken into account in interpreting the results of nonrandomized evaluations.

Fig. 18.10 shows the effect of the bias resulting from lead time on quantitative estimates of survival. Fig. 18.10A shows a situation in which no screening activity is being carried out. Five years after diagnosis, survival is 30%. If we institute a screening program with a 1-year lead time, the entire frame is shifted to the left (see Fig. 18.10B). If we now calculate survival at 5 years from the new time of diagnosis (see Fig. 18.10C), survival appears to be 50% but only as a result of lead time bias. The problem is that the apparently better survival is not a result of screened people living longer, but it is rather a result of a diagnosis being made at an earlier point in the natural history of their disease. For many diseases, such as cancer, the patient cannot die before the onset of the clinical phase and thus the time before early and usual diagnosis (i.e., the lead time) reflects what is also known as the "immortal time bias."

Consequently, in any comparison of screened and unscreened populations we must make an allowance for an estimated lead time in an attempt to identify any prolongation of survival above and beyond that resulting

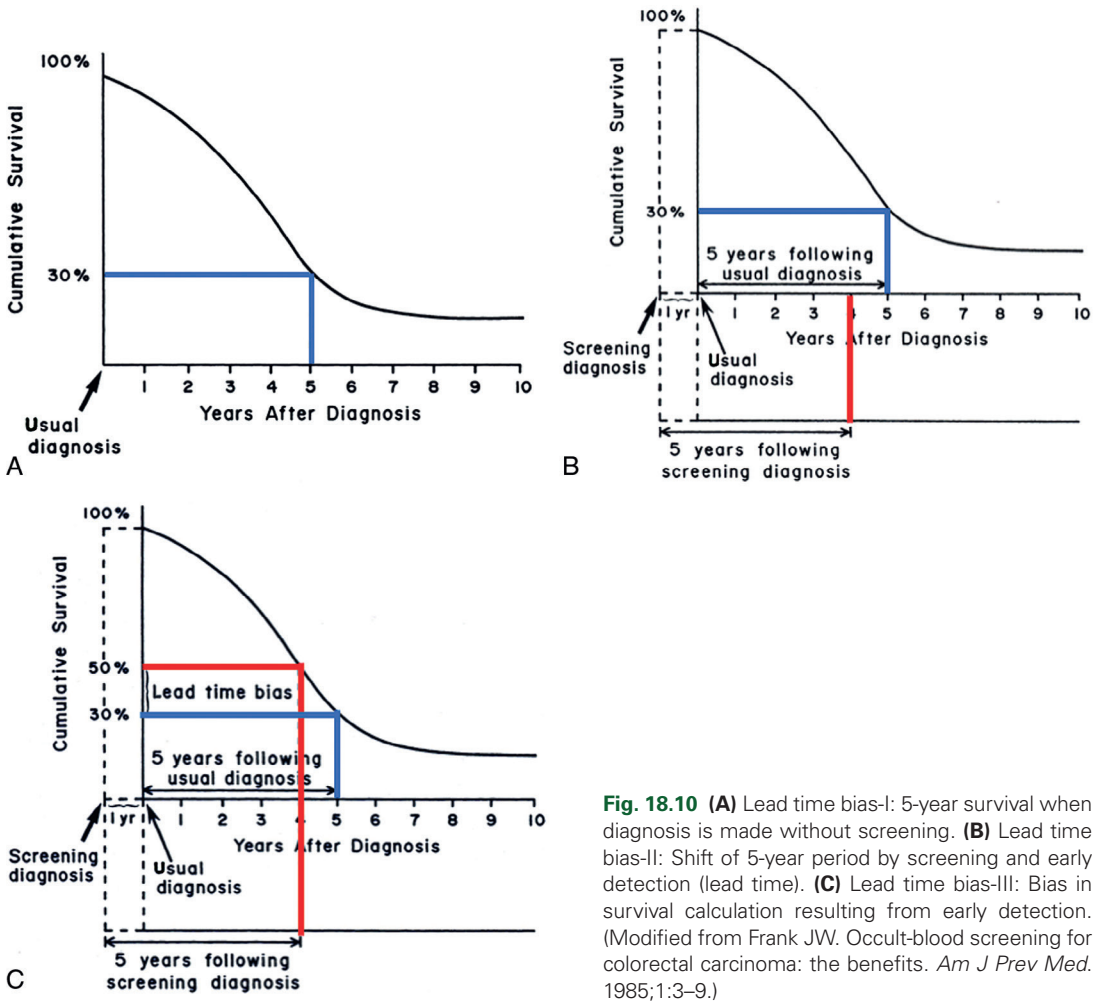

Fig. 18.10 **(A)** Lead time bias-I: 5-year survival when diagnosis is made without screening. **(B)** Lead time bias-II: Shift of 5-year period by screening and early detection (lead time). **(C)** Lead time bias-III: Bias in survival calculation resulting from early detection. (Modified from Frank JW. Occult-blood screening for colorectal carcinoma: the benefits. *Am J Prev Med.* 1985;1:3–9.)

from the artifact of lead time. If early detection is truly associated with improved survival, survival in the screened group should be greater than survival in the control group *plus the lead time.* We therefore have to generate some estimate of the lead time for the disease being studied.[5]

Another strategy is to compare mortality from the disease in the entire screened group with that in the unscreened group, rather than just the cumulative survival or its reciprocal, the case fatality rate, in those in whom disease was detected by screening.

Overdiagnosis Bias

Another potential bias is that of overdiagnosis. At times, people who initiate a screening program have almost limitless enthusiasm for the program. Even cytopathologists reading Pap smears for cervical cancer may become so enthusiastic that they may tend to overread the smears (in other words, to make false-positive readings). If they do overread, some normal women will be included in the group thought to have positive Pap smears. Consequently, the abnormal group will be diluted with women who are free of cancer. If normal individuals in the screened group are more likely to be erroneously diagnosed as positive than are normal individuals in the unscreened group (i.e., labeled as having cancer when in reality they do not), one could get a false impression of increased rates of detection and diagnosis of early-stage cancer as a result of the screening. In addition, because many of the persons with a diagnosis of cancer in the

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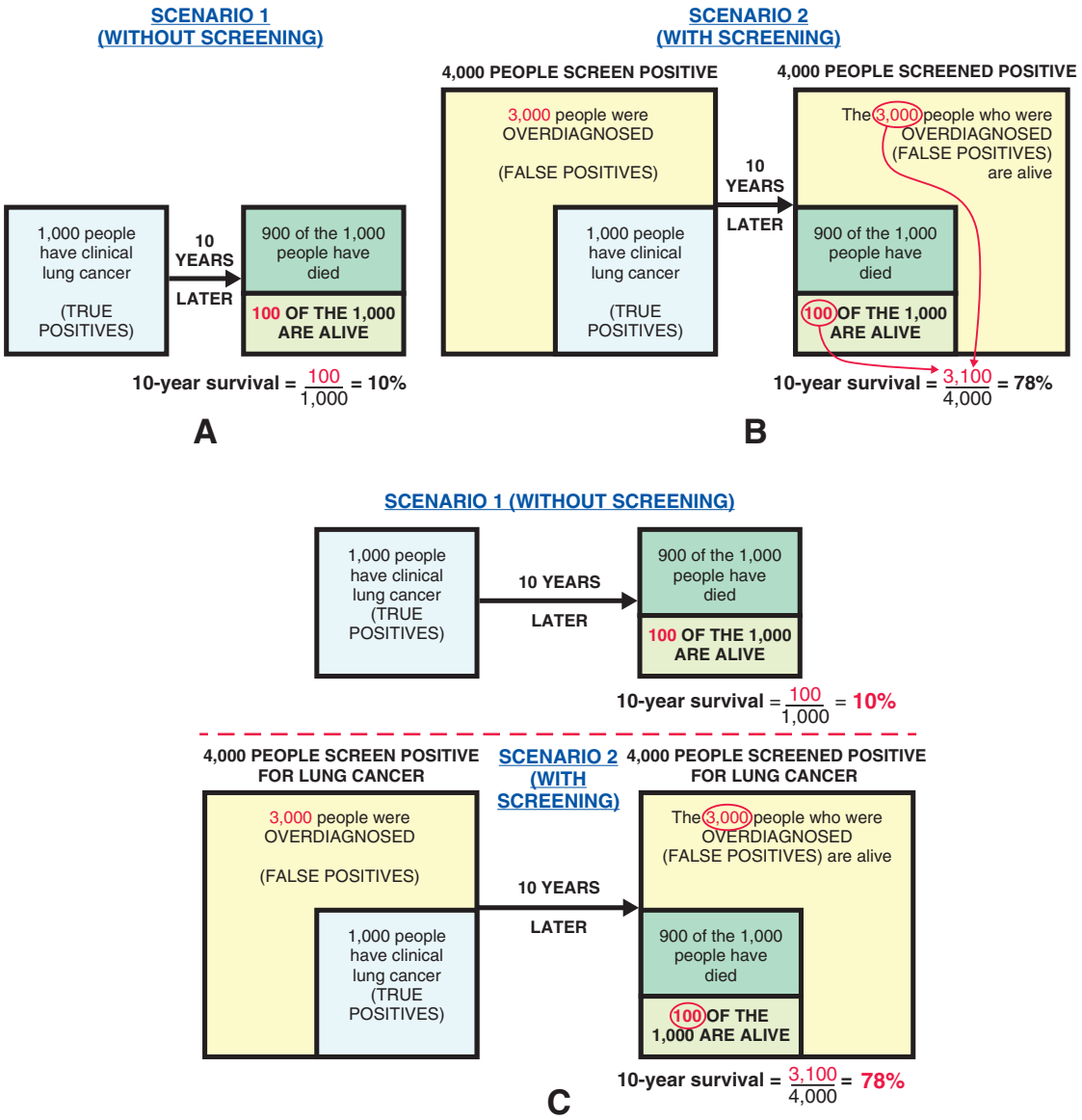

Fig. 18.11 The impact of overdiagnosis resulting from screening on estimation of survival. **(A)** Scenario 1—survival with no screening. **(B)** Scenario 2—when screening results in overdiagnosis: survival after 10 years. **(C)** Comparison of 10-year survival in Scenario 1 and Scenario 2. (Modified from Welch HG, Woloshin S, Schwartz LM. Overstating the evidence for lung cancer screening: the International Early Lung Cancer Action Program [I-ELCAP] study. *Arch Intern Med.* 2007;167:2289–2295.)

screened group would actually not have cancer and would therefore have a good survival, the results would represent an inflated estimate of survival after screening in persons thought to have cancer, resulting in a mistaken conclusion that screening had been shown to improve survival from cancer in this population.

The possible quantitative impact of overdiagnosis resulting from screening is demonstrated in a hypothetical example shown in Fig. 18.11. Fig. 18.11A shows Scenario 1, in which there is no screening. In this scenario, 1,000 patients with clinical lung cancer are followed for 10 years. At that point, 900 have died and

100 are alive. The 10-year survival for the 1,000 patients is therefore $\frac{100}{1,000}$, or 10%.

Fig. 18.11B shows Scenario 2, in which screening results in overdiagnosis. In this scenario, 4,000 people screen positive for lung cancer. Of these, 1,000 are the same patients with clinical lung cancer seen in Fig. 18.11A, and the other 3,000 are people who do not have lung cancer but are overdiagnosed by the screening test as being positive for lung cancer (false-positives).

After 10 years, these 3,000 people are still alive, as are the 100 people who had clinical lung cancer and survived as shown in Fig. 18.11A. The result is that of the 4,000 people who screened positive initially, 3,100 have survived for 10 years. As shown in the comparison of Scenario 1 and Scenario 2 in Fig. 18.11C, 10-year survival in Scenario 2 is now 78% compared with 10% in Scenario 1 in the original patient population of 1,000 who had clinical lung cancer. However, the apparently "better" survival seen in Scenario 2 is entirely due to the inclusion of 3,000 people who did not have lung cancer but were overdiagnosed by the screening method.

In effect, this is a misclassification bias, as discussed in Chapter 15. In this example, 3,000 people without lung cancer have been misclassified by the screening test as having lung cancer. Consequently, it is essential that in such studies of survival, the diagnostic process be rigorously standardized to minimize the potential problem of overdiagnosis.

STUDY DESIGNS FOR EVALUATING SCREENING: NONRANDOMIZED AND RANDOMIZED STUDIES

Nonrandomized Studies

In discussing the methodologic issues involved in nonrandomized studies of screening, we have in essence been discussing nonrandomized observational studies of screened and unscreened persons—a cohort design (Fig. 18.12).

The case-control design has also been used as a method of assessing the effectiveness of screening (Fig. 18.13). In this design the "cases" are people with advanced disease—the type of disease we hope to prevent by screening. Several proposals have been made for appropriate controls for such a study. Clearly, they should

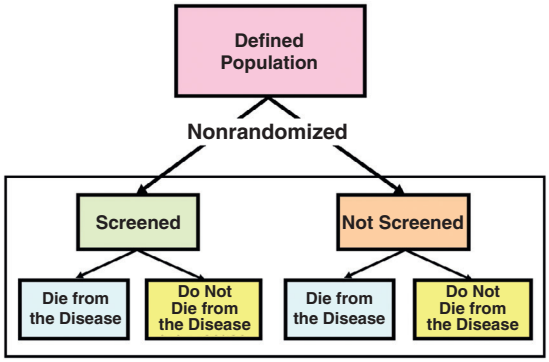

Fig. 18.12 Design of a nonrandomized cohort study of the benefits of screening.

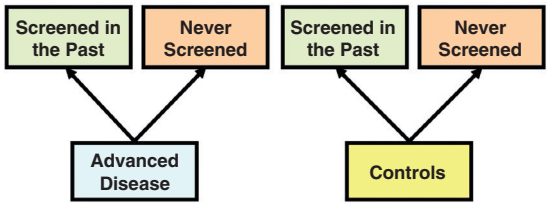

Fig. 18.13 Design of a case-control study of the benefits of screening.

be "non-cases" (i.e., people without advanced disease). Although the "controls" used in early case-control studies for evaluating screening were people with disease at an early stage, many researchers believe that people selected from the population from which the cases were derived are *better* controls. We then determine the prevalence of a history of screening among both the cases and the controls, so that screening is looked at as an "exposure." If screening is effective, we would expect to find a greater prevalence of screening history among the controls than among those with advanced disease, and an odds ratio can be calculated, which will be less than 1.0 if screening is effective.

Randomized Studies

In this type of study, a population is randomized, half to screening and half to no screening. Such a study is difficult to mount and carry out and may be fraught with ethical concerns. Perhaps the best known randomized trial of screening is the trial of screening for breast cancer using mammography that was carried out at the Health Insurance Plan (HIP) of New York.[6] Shapiro and colleagues conducted a randomized trial in women enrolled

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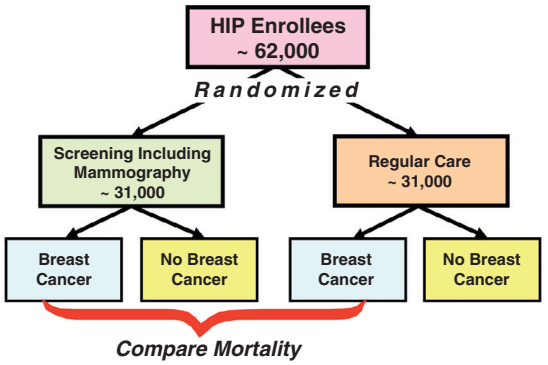

Fig. 18.14 Design of the Health Insurance Plan *(HIP)* randomized controlled trial begun in 1963 to study the efficacy of mammography screening. (Data from Shapiro S, Venet W, Strax P, et al., eds. *Periodic Screening for Breast Cancer: The Health Insurance Plan Project and Its Sequelae, 1963–1986*. Baltimore: Johns Hopkins University Press; 1988.)

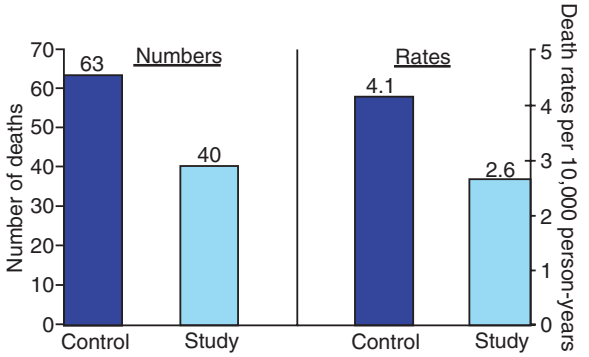

Fig. 18.15 Numbers of deaths due to breast cancer and mortality rates from breast cancer in control and study groups; 5 years of follow-up after entry into study. Data for study group include deaths among women screened and those who refused screening. (Data from Shapiro S, Venet W, Strax P, et al. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Natl Cancer Inst Monogr*. 1985;67:65–74.)

in the prepaid HIP program, an early health maintenance organization (HMO) in New York. This study has become a classic in the literature in reporting evaluation of screening benefits through a randomized trial design, and it serves as a model for future studies of this type.

The study was begun in 1963. It was designed to determine whether periodic screening using clinical breast examination by a physician and mammography reduced breast cancer mortality in women aged 40 to 64 years. Approximately 62,000 women were randomized into a study group and a control group of approximately 31,000 each (Fig. 18.14). The study group was offered screening examinations; 65% appeared for the first examination and were offered additional examinations at annual intervals. Most of these women had at least one of the three annual screening examinations that were offered. Screening consisted of physical breast examination, mammography, and interview. Control women received the usual medical care in the prepaid medical program. Many reports have been published from this outstanding study, and we will examine only a few of the results here.

Fig. 18.15 shows the number of breast cancer deaths and the mortality rates in both the study group (women who were offered screening mammography) and the control group after 5 years of follow-up.

Note that the data for the study group include deaths among women screened and those who refused screening. Recall the presentation on the problem of unplanned crossover in randomized trials. In that context, it was pointed out that the standard procedure in data analysis was to analyze according to the original randomization—an approach known as "intention to treat." That is precisely what was done here. Once a woman was randomized to mammography, she was kept in that group for purposes of analysis even if she subsequently refused screening. Despite this, we see that breast cancer deaths are much higher in the control group than in the study group.

Fig. 18.16 shows 5-year case-fatality in the women who developed breast cancer in both groups. The case-fatality in the control group was 40%. In the *total* study group (women who were randomized to receive mammography, regardless of whether or not they were actually screened) the case-fatality was 29%. To avoid lead time bias, the average breast cancer lead time was added to the survival of breast cancer patients in order to estimate the survival reciprocal, case-fatality. (Estimation of lead time bias in cancer is beyond the scope of this introductory textbook. It is discussed in Szklo M & Nieto FJ. *Epidemiology: Beyond the Basics*. 4th Edition. Jones & Bartlett, 2019). Shapiro and coworkers then divided this group into those who were screened and those who refused screening. In those who refused screening, the case-fatality was 35%. In those who were screened, the case-fatality was 23%.

Shapiro and colleagues then compared survival in women whose breast cancer was detected at the screening

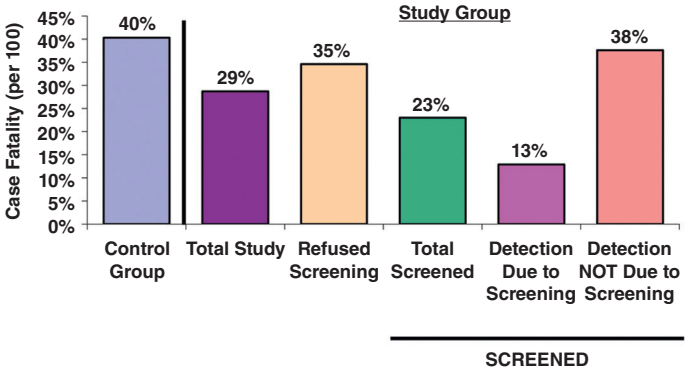

Fig. 18.16 Five-year case-fatality among patients with breast cancer. Case-fatality for those in whom detection was due to screening allow for a 1-year lead time. (Data from Shapiro S, Venet W, Strax P, et al. Ten- to 14-year effect of screening on breast cancer mortality. *J Natl Cancer Inst.* 1982;69:349–355.)

examination with that in women whose breast cancer was identified between screening examinations (i.e., no breast cancer was identified at screening, and before the next examination a year later, the women had symptoms that led to the diagnosis of breast cancer). If the cancer had been detected by mammography, the case-fatality was only 13%. However, if the breast cancer was an *interval case* (i.e., diagnosed between examinations), the case-fatality was 38%. What could explain this difference in case-fatality? The likely explanation is that disease that was found between regular mammographic examinations was rapidly progressive. It was not detectable at the regular mammographic examination but was identified before the next regularly scheduled examination a year later because it was so aggressive. (Another possibility is that at least some apparent interval cases were in reality cases that had not been detected at the previous screening examination [i.e., they were false negatives].)

These observations also support the notion discussed earlier in this chapter that a long clinical phase is likely to be associated with a long preclinical phase. Women in whom cancer findings were detected at screening had a long preclinical phase and a case-fatality of only 13%, indicating a long clinical phase as well. The women who had normal mammograms and whose disease became clinically apparent before the next examination had a short preclinical phase and, given the group's high case-fatality, also had a short clinical phase.

Fig. 18.17 shows deaths from causes *other than breast cancer* in both groups over 5 years. Mortality was much higher in those who did not come for screening than in those who did. Because the screening was only directed at breast cancer, why should those who came for screening and those who did not manifest different mortality

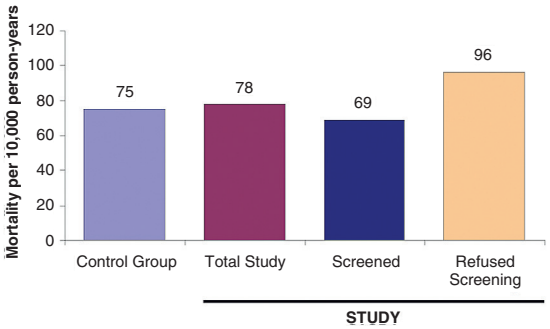

Fig. 18.17 Mortality from all causes *excluding breast cancer* per 10,000 person-years, Health Insurance Plan. (Data from Shapiro S, Venet W, Strax P, et al. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Natl Cancer Inst Monogr.* 1985; 67:65–74.)

rates for causes *other* than breast cancer? The answer is, clearly, volunteer bias—the well-documented observation that people who participate in health programs differ in many ways from those who do not: in their health status, attitudes, educational and socioeconomic levels, and other factors. This is another demonstration that for purposes of evaluating a health program, comparison of participants and nonparticipants is not a valid approach.

Before we leave our discussion of the HIP study, we might digress and mention an interesting application of these data carried out by Shapiro and coworkers.[7] Fig. 18.18 shows that, in the United States, 5-year relative survival from breast cancer is better in White than in Black women.

The question has been raised whether this is due to a difference in the biology of the disease in Black and

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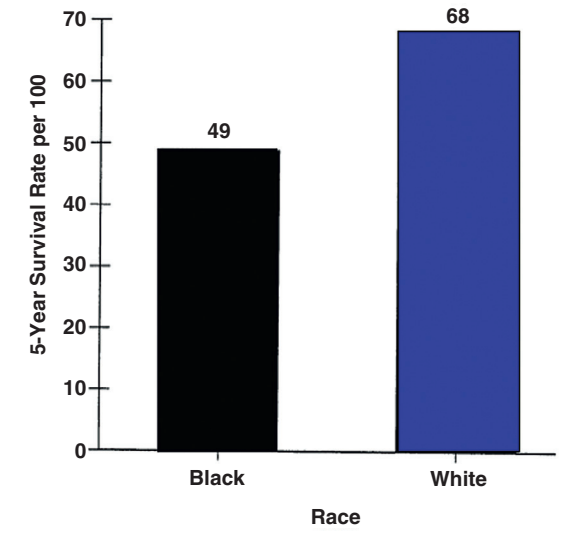

Fig. 18.18 Five-year relative survival rates, by race, among women with breast cancer diagnosed 1964–73 (Surveillance, Epidemiology, and End Results program). (Data from Shapiro S, Venet W, Strax P, et al. Prospects for eliminating racial differences in breast cancer survival rates. *Am J Public Health*. 1982; 72:1142–1145.)

White women or to a difference between Black and White people in accessing health care, which may delay the diagnosis and treatment of the disease in Black patients. Shapiro and colleagues recognized that the randomized trial of mammography offered an unusual opportunity to address this question. The findings are shown in Fig. 18.19. Let us first look only at the survival curves for the control group consisting of Black and White patients (see Fig. 18.19A). The data are consistent with those in Fig. 18.18: Black and Hispanic women had a worse prognosis than did White women. Now let us also look at the curves for White and Black women in the study group of women who were screened and for whom there was therefore no difference in access to care or use of care, because screening was carried out on a predetermined schedule (see Fig. 18.19B). We see considerable overlap of the two curves: essentially no difference. This strongly suggests that the screening had eliminated the racial difference in survivorship and that the usually observed difference between the races in prognosis of breast cancer is in fact a result of poorer access to care or poorer use of care among Black people,

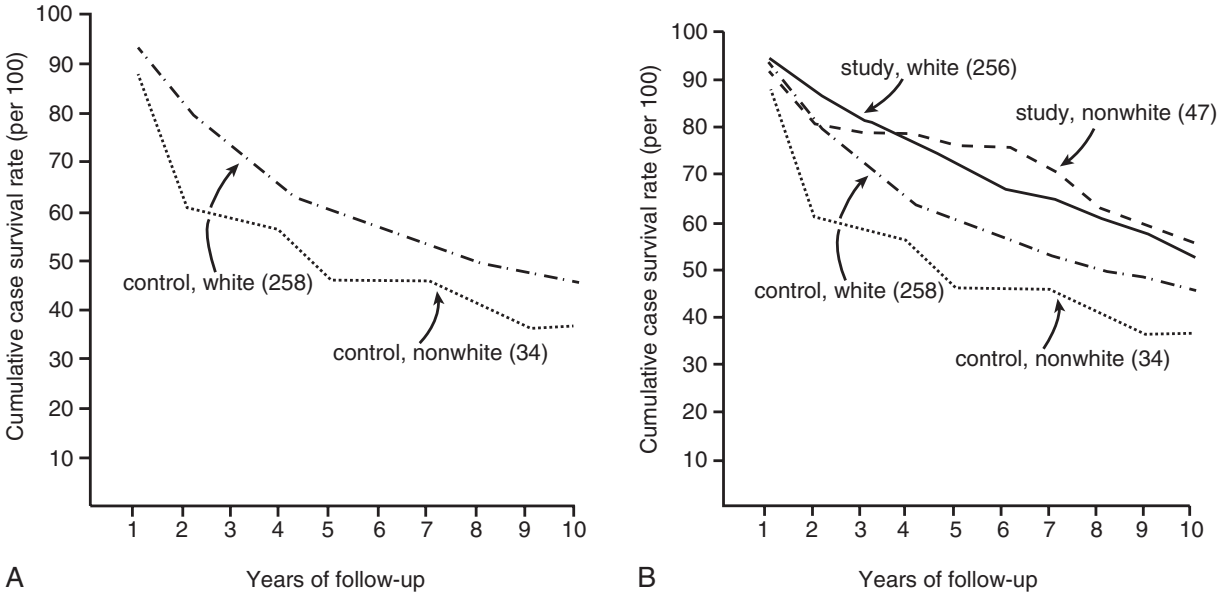

Fig. 18.19 **(A)** Cumulative case-survival rates, first 10 years after diagnosis by race, Health Insurance Plan (HIP) control groups. **(B)** Cumulative case-survival rates, first 10 years after diagnosis by race, HIP study and control groups. (From Shapiro S, Venet W, Strax P, et al. Prospects for eliminating racial differences in breast cancer survival rates. *Am J Public Health*. 1982;72:1142–1145.)

with a consequent delay in diagnosis and treatment, and hence survival.

Mammography for Women 40 to 49 Years of Age

A major controversy in the 1990s centered on the question of whether mammography should be universally recommended for women in their 40s. The data from the Shapiro et al. study, as well as from other studies, established the benefit of regular mammography examinations for women aged 50 years and older. However, the data are less clear for women in their 40s. Many issues arise in interpreting the findings of randomized trials carried out in a number of different populations. Although a reduction of mortality has been estimated at 17% for women in their 40s who have annual mammograms, the data available are generally from studies that were not specifically designed to assess possible benefits in this age group. Moreover, many of the trials recruited women in their *late* 40s, suggesting the possibility that even if there are observed benefits, they could have resulted just as well from mammograms performed when they would have been close to, or aged 50 years or older.

A related issue is seen in Fig. 18.20. When mortality over time is compared in screened and unscreened women *50 years of age or older* (see Fig. 18.20A), the mortality curves diverge at approximately 4 years after enrollment, with the mammography group showing a lower mortality that persists over time. However, when screened and unscreened *women in their 40s* are compared (see Fig. 18.20B), the mortality curves do not suggest any differences in mortality for at least 11 to 12 years after enrollment. Further follow-up will be needed to determine if the divergence observed in the mortality curves 11-12 years after enrollment would actually persist and represent a true benefit to women who have had mammograms in their 40s. However, interpreting these curves is complicated because women who have been followed for 10 or more years in these studies would have passed age 50. Consequently, even if mortality in screened women declines after 11–12 years, any such benefit observed could be due to mammograms that were performed *after* age 50 rather than to mammograms in their 40s. Further follow-up of women enrolled in many of these studies, and in newly initiated studies that are enrolling women in their early 40s, may help to clarify these issues.

In 1997 a consensus panel was created by the National Institutes of Health (lead by Professor Leon Gordis) to review the scientific evidence for benefits of mammography in women ages 40 to 49. The panel concluded that the data available *did not* warrant a universal recommendation for mammography for all women in their 40s. The panel recommended that each

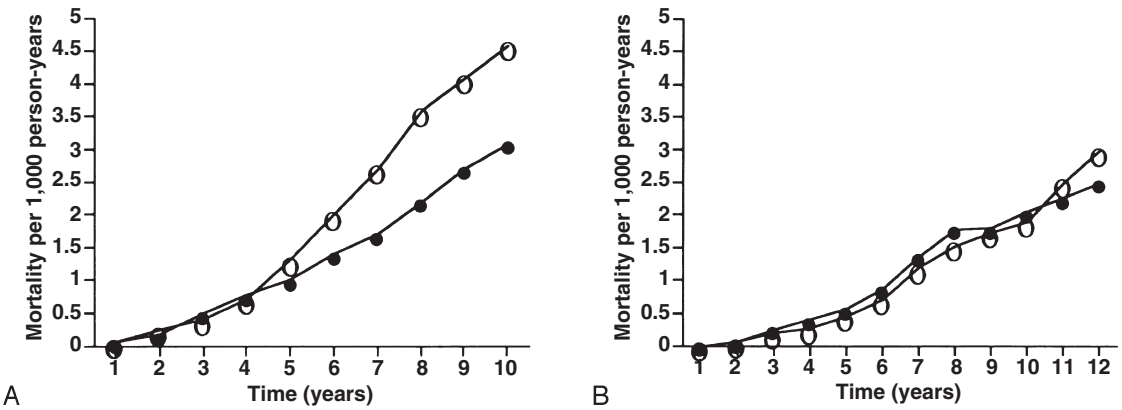

Fig. 18.20 Cumulative breast cancer mortality rates in screened and unscreened women **(A)** ages 50 to 69 years and **(B)** ages 40 to 49 years. • = screened; ○ = unscreened. (From Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49 years and 50 to 69 years: comparison of relative and absolute benefit. *Natl Cancer Inst Monogr.* 1997;22:79–86. [A] Modified from Tabar L, Fagerberg G, Duffy SW, et al. Update of the Swedish two-county program of mammographic screening for breast cancer. *Radiol Clin North Am.* 1992;30:187–210. [B] Modified from Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomized trials. *Lancet.* 1993;341:973–978.)

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woman should decide for herself (in consultation with her physician) whether to undergo mammography.[8] Her decision may be based not only on an objective analysis of the scientific evidence and consideration of her individual medical history, but also on how she perceives and weighs each potential risk and benefit, the values she places on each, and how she deals with uncertainty. Given both the importance and the complexity of the issues involved in assessing the evidence, a woman should have access to the best possible relevant information regarding both benefits and risks, presented in an understandable and usable form.

Most women will depend heavily on the knowledge and sophistication of their physicians rather than make the decision themselves on when to commence screening mammography. One important problem in this regard is that many physicians do not have sufficient knowledge of cancer screening statistics to provide the support needed by women and their families to carefully examine the results and conclusions, as well as the validity, of studies of mammography for women in their 40s. A study by Wegwarth and coauthors gave results of a national survey of primary care physicians in the United States and found that most primary care physicians mistakenly interpreted improved survival and increased detection with screening as evidence that screening saves lives. Few correctly recognized that reduced mortality in a randomized trial constitutes evidence of benefit of screening.[9]

The consensus panel added that for women in their 40s who choose to have mammography performed, the costs of the mammograms should be reimbursed by third-party payers or covered by HMOs so that financial impediments will not influence a woman's decision as to whether or not to have a mammogram. The recommendations of the panel were rejected by the National Cancer Institute, which had itself originally requested creation of the panel, and by other agencies. There were clear indications that strong political forces were operating at that time in favor of mammography for women in their 40s.

The controversy over mammography became an even broader one with the 2001 publication of a review by Olsen and Gøtzsche of the evidence supporting mammography *at any age.*[10] Among the issues raised by the investigators were concerns about possible inadequacy of some of the randomizations; possible unreliability of assessment of cause of death; their finding that in some trials exclusions of women from the studies were carried out after randomization had taken place and women with preexisting cancer were excluded only from the screened groups; and their assessment that the two best trials failed to find any benefit.

An accompanying *Lancet* editorial concluded by saying: "*At present, there is no reliable evidence from large randomized trials to support screening mammography programmes.*"[11] A 2004 article countered the arguments raised by Olsen and Gøtzsche and concluded that the prior consensus on mammography was correct.[12]

However, the controversy continues unabated. In 2002 the US Preventive Services Task Force reviewed the evidence and recommended screening mammography every 1 to 2 years for women 40 years of age and older. Using an earlier version of the methodology than that described in Chapter 14, they classified the supporting evidence as "fair" on a scale of "good," "fair," or "poor."[13] In 2009 this task force again reviewed the question of mammography for women in their 40s and recommended that women aged 50 to 74 years should have screening mammography every 2 years, but they also concluded as follows: "*For biennial screening mammography in women aged 40 to 49 years, there is moderate certainty that the net benefit is small.*" The task force gave its recommendation a "C" grade and pointed out that this grade is a recommendation against routine screening of women aged 40 to 49 years. They added, "*The Task Force encourages individualized, informed decision making about when [at what age] to start mammography screening.*"[14] The "C" grade was confirmed in a more recent recommendation statement from the task force.[15]

In 2007 the American College of Physicians published new guidelines about mammography for women in their 40s, based on an extensive systematic review that addressed both benefits and potential harms.[16,17] The group concluded that the evidence of net benefit is *less clear* for women in their 40s than for women in their 50s and that mammography carries significant risks, saying: "*We don't think the evidence supports a blanket recommendation.*" These risks include anxiety from false positivity and a small dose of ionizing radiation exposure in addition to the small environmental radiation exposure). In 2011 the National Health Service in the United Kingdom issued its guidelines recommending that women aged 47 to 73 years undergo mammography every 3 years.[18]

In 2015 the American Cancer Society (ACS) updated its guidelines for breast cancer screening for women at "average risk."[19] The ACS recommended starting screening at age 45 years, with annual screening through age 54, after which biennial screening should be considered. In May 2023, the US Preventive Services Task Force published an interim recommendation that all women should get screened for breast cancer biannually, starting at age 40. The recommendation was for women at average risk, including those with a family history of breast cancer and other risk factors such as dense breasts. They particularly noted the importance of mammography for Black females. The draft recommendation has a grade of B. https://www.uspreventiveservicestaskforce.org/uspt/draft-recommendation.org/breast-cancer-screening-adults. As is clear, this is not an area where science, epidemiology, and public policy are totally aligned!

Thus, the controversy between proponents and critics continues and is not likely to be settled to everyone's satisfaction by expert pronouncements. The problems in methodology and interpretation are complex and will probably not be resolved by further large trials. Such trials are difficult and expensive to initiate and conduct, and because of the time needed to complete them, these trials are also limited in that the findings often do not reflect the most recent improvements in mammographic technology. However, with so much of the data equivocal and a focus of controversy, progress will most likely come from new and better technologies for detecting breast cancer in a valid and reliable way.

Further Examples of Studies Evaluating Screening

Screening Strategies for COVID-19

In late 2019, a new strain of coronavirus emerged as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused coronavirus disease (COVID-19). It was prudent to the medical, scientific, and public health communities to expedite the development of strategies not only to screen for the presence of the virus, but also to manage, treat, and ultimately prevent COVID-19 or reduce its severity and risk of complications. Given the fast spread and the case fatality of COVID-19, the World Health Organization identified COVID-19 as a Public Health Emergency of International Concern, which later was formally classified as a pandemic. In the meantime, it may not have been suitable to run randomized trials with a view towards issuing guidelines by Public Health organizations (e.g., WHO, CDC, etc.). At that time, COVID-19 screening guidelines were emerging based on what we knew about earlier strains of coronaviruses, and subsequently on observational studies based on natural experiments. As our knowledge and experience on COVID-19 emerged, screening guidelines evolved as well. Furthermore, such guidelines evolved as COVID-19 vaccines and treatments were developed and approved by regulatory authorities.

Identifying the different elements of COVID-19 screening has been a multifaceted, complex process and evolving workstream; we need to know who to screen, when to screen, how to screen, and what to do with a test result. The CDC offered printable, public-friendly guidelines (Fig. 18.21) to rally the public behind the healthcare professionals in implementing such screening strategies.

Who to screen. Should we screen everyone? Should we screen anyone who wants to be screened even if they do not have a history of exposure to an individual with a confirmed positive COVID-19 test? These were pressing public health questions, especially when the world was taken by surprise and a huge strain was imposed on the health care systems worldwide. Such guidelines differed according to the target population and local settings, i.e., the general public, individuals with high risk to severe COVID-19, school students and staff, health care workers, and frontline first responders, etc. Each of these guidelines must weigh in the benefit of screening for these individuals and the risk of either getting a false positive (or a false negative) test result, resource allocation, and loss of productivity.

When to screen. In order to optimize and properly allocate resources, the CDC advises that the test be done if (1) an individual has COVID-19 symptoms, (2) 5 full days after being exposed to COVID-19 and does not have symptoms, or (3) if at high risk for severe COVID-19 (e.g., defined by presence of comorbid conditions) while being in an area with a medium or high COVID-19 Community Level.[20]

How to screen. Viral tests have a higher sensitivity to detect positive cases, but several types of virus exist, the most common being nucleic acid amplification tests (NAATs), such as PCR-based tests, and antigen tests. The PCR test, the most valid, is done in the laboratory, and it takes approximately 24 hours to get the results. On the other hand, antigen tests are much faster (results can be obtain in 15 minutes) but much less valid. It is also worth mentioning that antibody-related (serology) tests can only be used to denote the presence of antibodies in the blood, which can either reflect a prior

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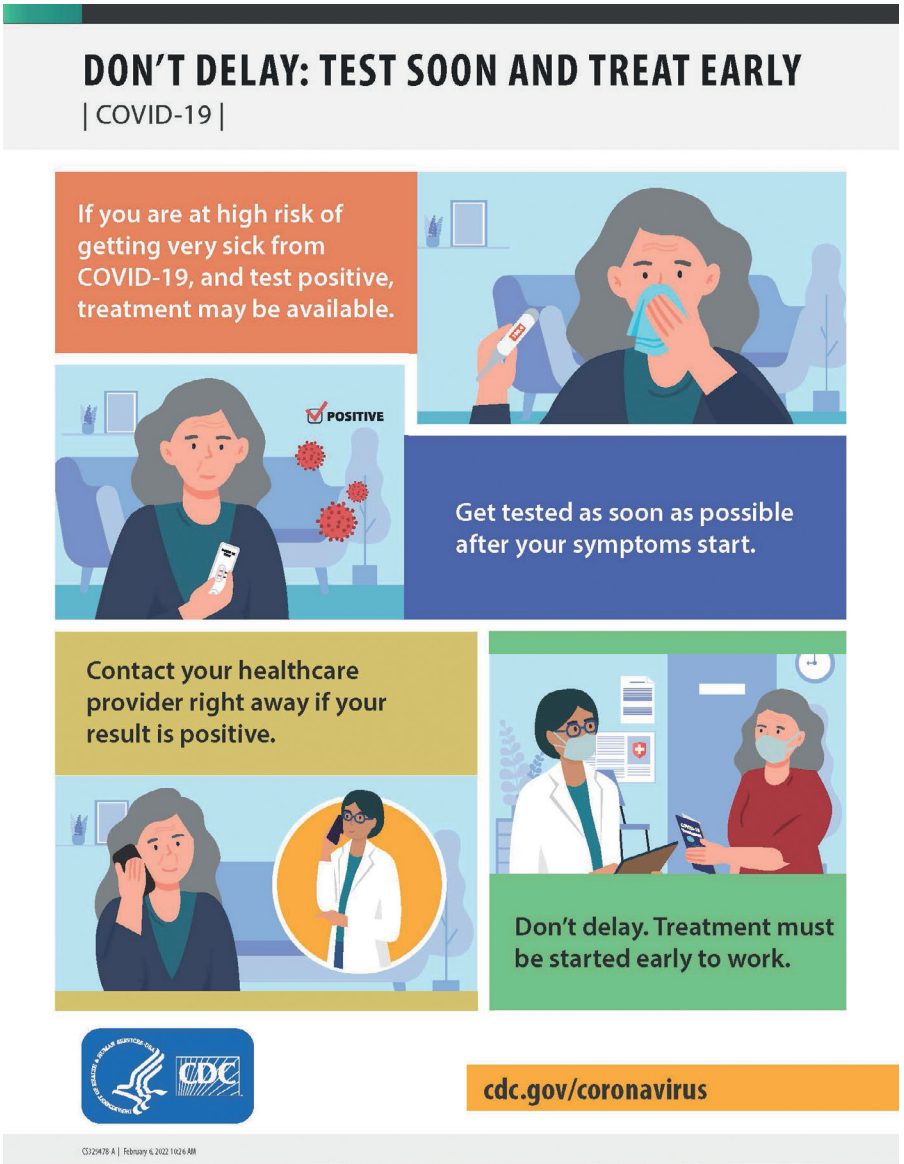

Fig. 18.21 CDC guidelines for COVID-19 screening strategies. (From Center for Disease Control and Prevention. Covid-19 Print Resources. Feb 4, 2022. https://www.cdc.gov/coronavirus/2019-ncov/communication/print-resources.html)

infection or vaccination, and they should not be used to screen for active COVID-19 infection.

What to do with a test result. The CDC guidelines[20] for COVID-19 recommend isolation, advising contacts to get tested, seeking an emergency room visit if warning signs are developed (Fig 18.22), and contacting health care providers to explore treatment options, among others. On the other hand, a negative test does nor rule out active infection, but the CDC recommends that if the individual has symptoms or has been exposed to a confirmed positive case, general public health precautions should be followed and the health care provider should be contacted. If the individual does not have symptoms, the guideline is to resume normal activities.

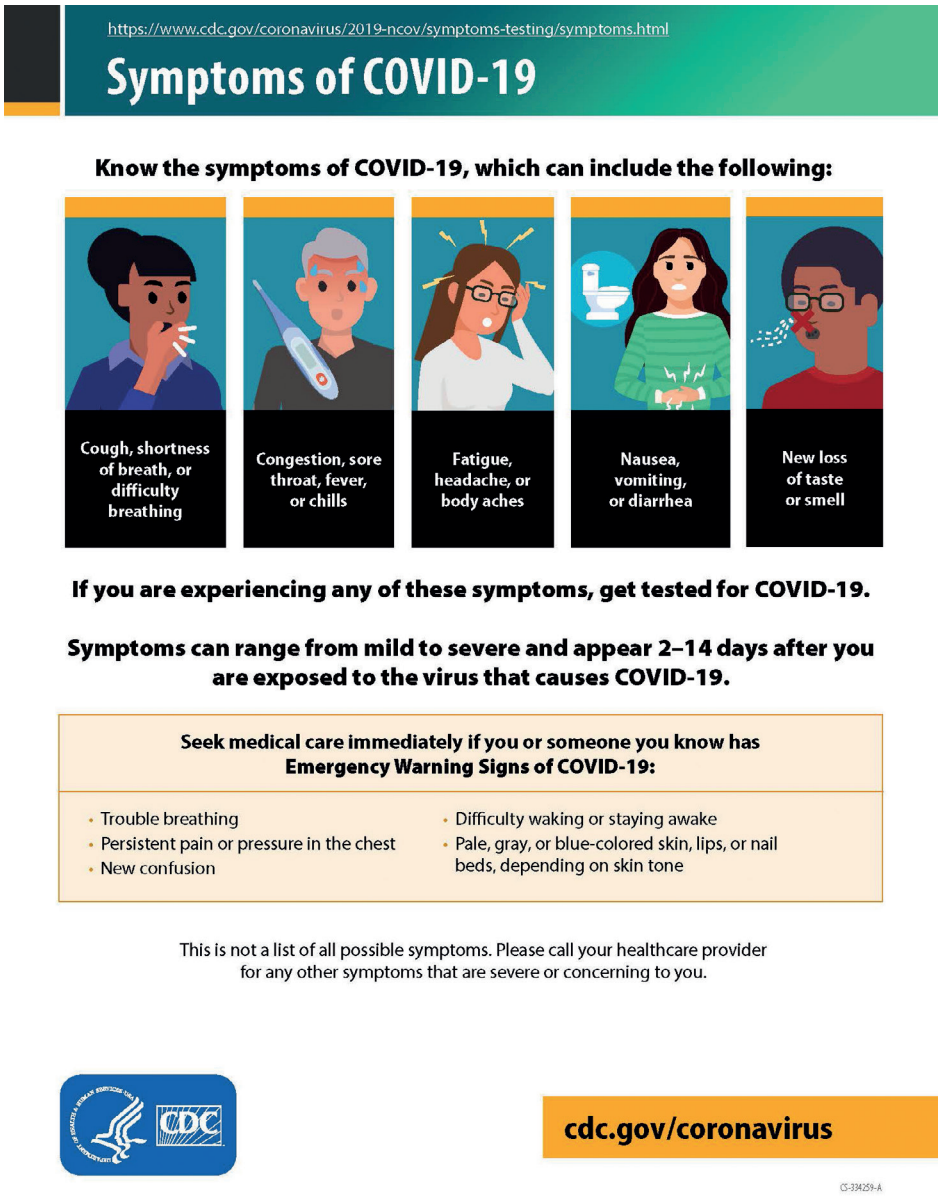

Fig. 18.22 CDC guidelines for COVID-19 Symptoms. (From Center for Disease Control and Prevention. Covid-19 Print Resources. March 18, 2021. https://www.cdc.gov/coronavirus/2019-ncov/communication/print-resources.html)

Screening for Cervical Cancer

Perhaps no screening test for cancer has historically been used more widely than the Pap smear. One would therefore assume that there has been overwhelming evidence of its effectiveness in reducing mortality from invasive cervical cancer. However, there has never been a properly designed randomized, controlled trial of cervical cancer screening; there probably never will be, because cervical cancer screening has been accepted as effective for the early detection of cervical cancer both by health authorities and by women.

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In the absence of randomized trials, several alternative approaches have been used. Perhaps the most frequent evaluation design has been to compare incidence and mortality rates in populations with different rates of screening. A second approach has been to examine changes over time in rates of diagnosis of carcinoma in situ. A third approach has been that of case-control studies in which women with invasive cervical cancer are compared with control women and the frequency of past Pap smears is examined in both groups. All of these studies are generally affected by the methodologic problems raised previously in this chapter. Given the recognition that HPV is in the causal chain to cervical cancer, prevention currently recommends HPV testing along with Pap testing. The ACS recommends starting screening at age 21 with annual Pap tests (either conventional cytology or liquid based), with HPV testing started at age 30 or the use of high-risk HPV screening alone.[21] However, even for high risk HPV types, infection may revert after HPV screening alone, resulting in a large number of false-positives. Accordingly, the US Preventive Services Task Force recommends screening in women aged 21 to 65 years with cytology (Pap test) every 3 years or, for women aged 30 to 65 years who want a less frequent screening, cytology combined with HPV every 5 years.[4]

Despite these reservations, the evidence indicates that many carcinomas in situ probably do progress to invasive cancer; consequently, early detection of cervical cancer in the in situ stage would result in a significant saving of life, even if it is lower than many optimistic estimates. Much of the uncertainty we face regarding screening for cervical cancer stems from the fact that no well-designed randomized trial was initially carried out before it became part of routine medical practice. This observation points out that in the United States, a set of standards must be met before new pharmacologic agents are licensed for human use, but another, less stringent, set of standards is used for new technology or new health programs. No drug would be licensed in the United States without evaluation through randomized, controlled trials, but unfortunately no such evaluation is required before screening or other types of programs and procedures are introduced. Of course, if universal prevention of HPV through vaccination of pre–sexually active adolescents was applied, cervical cancer would end!

Screening for Neuroblastoma

Some of the issues just discussed are encountered in screening for neuroblastoma, which is a tumor that occurs in young children. The rationale for screening for neuroblastoma was outlined by Tuchman and colleagues[22]: (1) Outcome has improved little in the past several decades. (2) Prognosis is known to be better in children who manifest the disease before the age of 1 year. (3) At any age, children in advanced stages of disease have worse prognoses than those in early stages. (4) More than 90% of children presenting with clinical symptoms of neuroblastoma excrete higher than normal amounts of catecholamines in their urine. (5) These metabolites can easily be measured in urine samples obtained from diapers.

These facts constitute a strong rationale for neuroblastoma screening. Fig. 18.23 shows data from Japan,

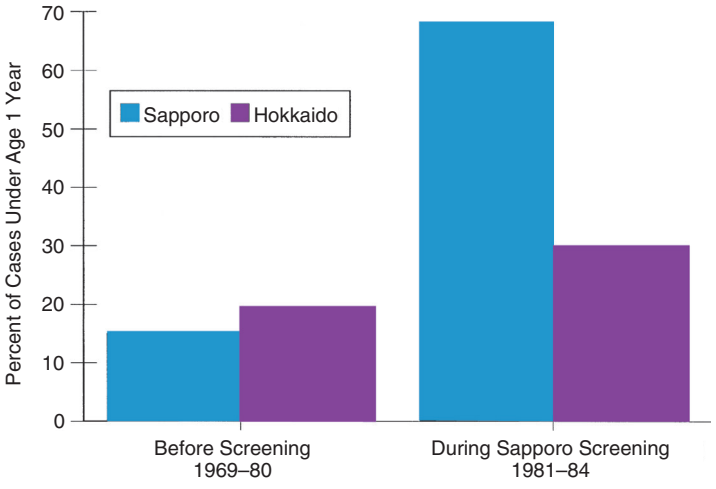

Fig. 18.23 Percentage of neuroblastoma cases younger than 1 year in Sapporo and Hokkaido, Japan, before and after screening. (Modified from Goodman SN. Neuroblastoma screening data: an epidemiologic analysis. *Am J Dis Child*. 1991;145:1415–1422; Based on data from Nishi M, Miyake H, Takeda T, et al. Effects of the mass screening of neuroblastoma in Sapporo City. *Cancer*. 1987;60:433–436. Copyright © 1987 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

where a major effort at neuroblastoma screening was mounted. The percentages of children younger than 1 year in whom neuroblastoma was detected were compared before and after initiation of screening in Sapporo, a city in Hokkaido, and these data were compared with birth data from the rest of Hokkaido, where no screening program was mounted. After initiation of screening, a greater percentage of cases of neuroblastoma in children younger than 1 year was detected in Sapporo than in the rest of Hokkaido.

However, a number of serious problems arise in assessing the benefits of neuroblastoma screening. It is now clear that neuroblastoma is a biologically heterogeneous disease, and there is clearly a better prognosis from the start in some cases than in others. Many tumors have a good prognosis because they regress spontaneously, even without treatment. Furthermore, screening is most likely to detect slow growing, less malignant tumors and is less likely to detect aggressive, fast-growing tumors.

Thus, it is difficult to show that screening for neuroblastomas is, in fact, beneficial. In fact, two large studies of neuroblastoma screening appeared in 2002. Woods and colleagues[23] studied 476,654 children in Quebec, Canada. Screening was offered to all the children at ages 3 weeks and 6 months. Mortality from neuroblastoma up to 8 years of age among children screened in Quebec was no lower than among four unscreened cohorts (Table 18.1) and no lower than in the rest of Canada, excluding Quebec, and in two historical cohorts (Table 18.2). Schilling and colleagues[24] studied 2,581,188 children in Germany who were offered screening at 1 year of age. They found that neuroblastoma screening did not reduce the incidence of disseminated disease and did not appear to reduce mortality from the disease, although mortality follow-up was not yet complete. Thus the data currently available do not support screening for neuroblastoma. The findings in these studies demonstrate the importance of understanding the biology and natural history of the disease and the need to obtain relevant and rigorous evidence regarding the potential benefits or lack of benefits when screening for any disease is being considered. The ability to detect a disease by screening cannot be equated with a demonstration of benefit to those screened.

TABLE 18.1 Rate of Death From Neuroblastoma by 8 Years of Age in the Screened Quebec Cohort, as Compared With the Rates in Four Unscreened Cohorts

Control Cohort	No. of Deaths Expected in Quebec Based on the Control Cohort	Standardized Mortality Ratio for Quebec (95% CI)
Ontario	19.8	1.11 (0.64–1.92)
Minnesota	24.4	0.90 (0.48–1.70)
Florida	15.7	1.40 (0.81–2.41)
Greater Delaware Valley	22.8	0.96 (0.56–1.66)

There were 22 deaths due to neuroblastoma in the screened Quebec cohort.
CI, Confidence interval.
From Woods WG, Gao R, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med.* 2002;346:1041–1046.

TABLE 18.2 Rate of Death From Neuroblastoma by 8 Years of Age in the Screened Quebec Cohort, as Compared With the Rates in Unscreened Canadian Cohorts

Control Cohort	No. of Deaths Expected in Quebec Based on the Control Cohort	Standardized Mortality Ratio for Quebec (95% CI)
Historical Cohorts		
Quebec	22.5	0.98 (0.54–1.77)
Canada	21.2	1.04 (0.64–1.69)
Concurrent Cohort		
Canada, excluding Quebec	15.8	1.39 (0.85–2.30)

There were 22 deaths from neuroblastoma in the screened cohort. All data were collected by Statistics Canada.
CI, Confidence interval.
From Woods WG, Gao R, Shuster JJ, et al. Screening of infants and mortality due to neuroblastoma. *N Engl J Med.* 2002;346:1041–1046.

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PROBLEMS IN ASSESSING THE SENSITIVITY AND SPECIFICITY OF SCREENING TESTS

New screening programs are often initiated after a screening test first becomes available. When such a test is developed, claims are often made—by manufacturers of test kits, investigators, or others—that the test has high sensitivity and a high specificity. However, as we shall see, from a practical standpoint, this may often be difficult to demonstrate.

Fig. 18.24A shows a 2 × 2 table, as we have seen in earlier chapters, tabulating reality (disease present or absent) against test results (positive or negative).

To calculate sensitivity and specificity, data are needed in all four cells. However, often only those with positive test results ($a + b$) (seen in the *upper row* of the figure) are sent for further testing. Data for those who test negative ($c + d$) are frequently not available, because these patients do not receive further testing. For example, as shown in Fig. 18.24B, the Western blot test serves as a gold standard for detecting human immunodeficiency virus (HIV) infection, and those with positive enzyme-linked immunosorbent assay (ELISA) results are sent for Western blot testing.

However, because those with negative ELISA results are generally not tested further, the data needed in the lower cells for calculating sensitivity and specificity of the ELISA are often not available from routine testing. To obtain such data, it is essential that some negative ELISA specimens also be sent for further testing, together with the ELISA-positive specimens.

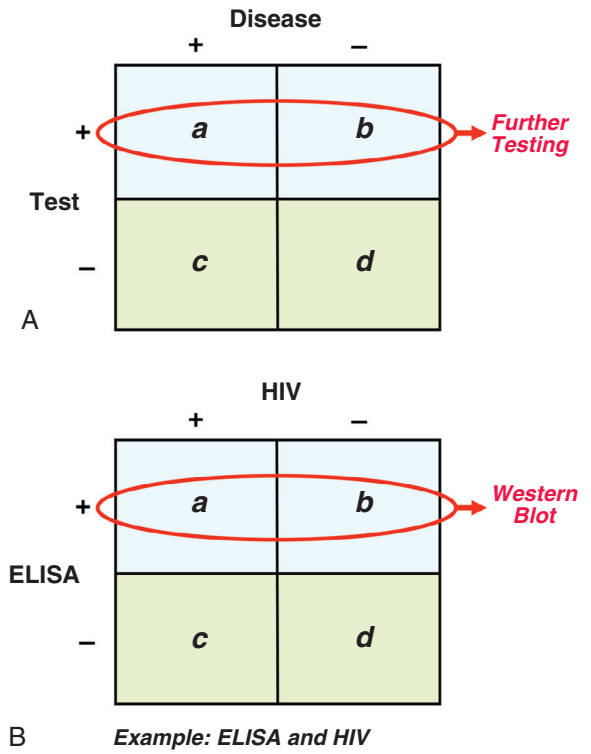

Fig. 18.24 **(A)** Problem of establishing sensitivity and specificity because of limited follow-up of those with negative test results. **(B)** Problem of establishing sensitivity and specificity because of limited follow-up of those with negative test results for human immunodeficiency virus (HIV) using the enzyme-linked immunosorbent assay (ELISA) test.

INTERPRETING STUDY RESULTS THAT SHOW NO BENEFIT OF SCREENING

In this chapter, we have stressed the interpretation of results that show a difference between screened and unscreened groups. However, if we are unable to demonstrate a benefit from early detection of disease, any of the following interpretations may be possible:

1. The apparent lack of benefit may be inherent in the natural history of the disease (e.g., the disease has no detectable preclinical phase or an extremely short detectable preclinical phase).
2. The therapeutic intervention currently available may not be any more effective when it is provided earlier than when it is provided at the time of usual diagnosis.
3. The natural history and currently available therapies may have the potential for enhanced benefit, but inadequacies of the care provided to those who screen positive may account for the observed lack of benefit (i.e., there is efficacy but poor effectiveness).

COST-BENEFIT ANALYSIS OF SCREENING

Some people respond to cost-benefit issues by concentrating only on cost, asking, if the test is inexpensive, why not perform it? However, although the test for blood in the stool, for example, in screening for colon cancer, costs only a few dollars for the filter paper kit and the necessary laboratory processing, to calculate the total cost of such a test we must include the cost of the colonoscopies that are done after the initial testing

BOX 18.3 Criteria Used by the American Cancer Society for Recommendations on Cancer-Related Checkups

1. There must be good evidence that each test or procedure recommended is medically effective in reducing morbidity or mortality.
2. The medical benefits must outweigh the risks.
3. The cost of each test or procedure must be reasonable compared with its expected benefits.
4. The recommended actions must be practical and feasible.

for those who are detected as "positive," as well as the cost of the complications that infrequently result from colonoscopy.

The balance of cost effectiveness includes not only financial costs but also nonfinancial costs to the patient, including anxiety, emotional distress, inconvenience, and the disruption it may make to the patient's daily life and/or his family or caregivers. Is the test itself invasive? Even if it is not, if the test result is positive, is invasive therapy warranted by the test result? What is the false-positive rate in such tests? In what proportion of persons will invasive tests be carried out or anxiety be generated despite the reality that the individuals do not have the disease in question? Thus the "cost" of a test is not only the cost of the test procedure but also the cost of the entire follow-up process that is set in motion by a positive result, even if it turns out to be a false-positive result. These considerations are reflected in the four major concerns voiced by the ACS in revising its guidelines for cancer screening (Box 18.3).[25]

CONCLUSION

This chapter has reviewed some of the major sources of bias that must be taken into account in assessing study findings that compare screened and unscreened populations. The biases of selection for screening and prognostic selection can be addressed, in large part, by using a randomized, controlled trial as the study design. Reasonable estimates of the lead time can be made if appropriate information is available. Few of the methods that are currently used to detect disease early have been subjected to evaluation by randomized trials, and most are probably not destined to be studied in this way. This is a result of several factors, including the difficulty and expense associated with conducting such studies and the ethical issues inherent in randomizing a population to receive or not receive modalities of care that are widely used and considered effective, even in the absence of strong supporting evidence. Consequently, we are obliged to maximize our use of evidence from nonrandomized approaches, and to do so, the potential biases and problems addressed in this chapter must be considered.

In approaching programs for early disease detection, we need to be able to identify groups who are at high risk. This would include not only those at risk for developing the disease in question but also those who are "at risk" for benefiting from the intervention. These are the groups for whom cost-benefit calculations will favor benefit. We must keep in mind that, even if a screening test, such as a Pap smear, is not in itself overly invasive, the intervention mandated by a positive screening test result may be highly invasive.

The overriding issue is how to make decisions when our data are inconclusive, inconsistent, or incomplete. We face this dilemma regularly, both in in the development of public health policy and in clinical practice. These decisions must first consider the existing body of relevant scientific evidence. However, in the final analysis, the decision whether or not to screen a population for a disease is a *value judgment* that should take into account the incidence and severity of the disease, the feasibility of detecting the disease early, the likelihood of intervening effectively in those with positive screening results, and the overall cost-benefit calculation for an early detection program.

To improve our ability to make appropriate decisions, additional knowledge is needed regarding the natural history of disease and, specifically, regarding the definition of characteristics of individuals who are at risk for a poor outcome. Before new screening programs are introduced, we should argue strongly for well-conducted randomized, controlled trials, so that we will not be operating in an atmosphere of uncertainty at the time in the future when such trials have become virtually impossible to conduct. Nevertheless, given the fact that most public health and medical practices—including early detection of disease—have not been subjected to randomized trials and that decisions regarding early detection must be made on the basis of incomplete and

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equivocal data, it is essential that we as health professionals appreciate and understand the methodologic issues involved so that we can make the wisest use of the available knowledge on behalf of our patients. Even the best of intentions and passionate evangelism cannot substitute for rigorous evidence that supports or does not support the benefit of screening.

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REVIEW QUESTIONS FOR CHAPTER 18

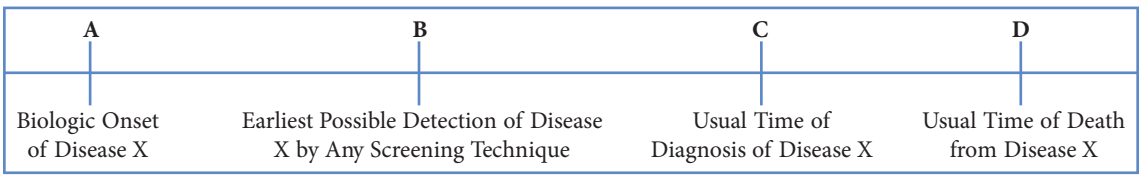
Questions 1 through 4 are based on the following information:

A new screening program was instituted in a certain country. The program used a screening test that is effective in detecting cancer Z at an early stage. Assume that there is no effective treatment for this type of cancer and therefore that the program results in no change in the usual course of the disease. Assume also that the rates noted are calculated from all known cases of cancer Z and that there were no changes in the quality of death certification of this disease.

1. *What will happen to the apparent incidence rate of cancer Z in the country during the first year of this program?*
   - **a.** Incidence rate will increase
   - **b.** Incidence rate will decrease
   - **c.** Incidence rate will remain constant
2. *What will happen to the apparent prevalence rate of cancer Z in the country during the first year of this program?*
   - **a.** Prevalence rate will increase
   - **b.** Prevalence rate will decrease
   - **c.** Prevalence rate will remain constant
3. *What will happen to the apparent case-fatality for cancer Z in the country during the first year of this program?*
   - **a.** Case-fatality will increase
   - **b.** Case-fatality will decrease
   - **c.** Case-fatality will remain constant
4. *What will happen to the apparent mortality rate from cancer Z in the country as a result of the program?*
   - **a.** Mortality rate will increase
   - **b.** Mortality rate will decrease
   - **c.** Mortality rate will remain constant
5. *The best index (indices) for concluding that an early detection program for breast cancer truly improves the natural history of disease, 15 years after its initiation, would be:*
   - **a.** A smaller proportionate mortality for breast cancer 15 years after initiation of the early detection program compared to the proportionate mortality prior to its initiation
   - **b.** Improved long-term survival rates for breast cancer patients (adjusted for lead time)
   - **c.** A decrease in incidence of breast cancer
   - **d.** A decrease in the prevalence of breast cancer
   - **e.** None of the above
6. *In general, screening should be undertaken for diseases with the following feature(s):*
   - **a.** Diseases with a low prevalence in identifiable subgroups of the population
   - **b.** Diseases for which case-fatality is low
   - **c.** Diseases with a natural history that can be altered by medical intervention
   - **d.** Diseases that are readily diagnosed and for which treatment efficacy has been shown to be equivocal in evidence from a number of clinical trials
   - **e.** None of the above

Question 7 is based on the information given below:

The diagram below shows the natural history of disease X:



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7. *Assume that early detection of disease X through screening improves prognosis. For a screening program to be most effective, at which point in the natural history in the diagram must the critical point be?*

a. Between A and B
b. Between B and C
c. Between C and D
d. Anywhere between A and C
e. Anywhere between A and D

8. *Which of the following is not a possible outcome measure that could be used as an indicator of the benefit of screening programs aimed at early detection of disease?*

a. Reduction of case-fatality in screened individuals
b. Reduction of mortality in the population screened
c. Reduction of incidence in the population screened
d. Reduction of complications
e. Improvement in the quality of life in screened individuals

19

Epidemiology and Public Policy

All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.[1]
—Sir Austin Bradford Hill, President's Address, Royal Society of Medicine, January 14, 1965

Experience is that marvelous thing that enables you to recognize a mistake when you make it again.[2]
—Franklin P. Jones, legendary American humorist (1908–1980)

LEARNING OBJECTIVES

- To review the role of epidemiology in disease prevention and to contrast two possible strategies for prevention: targeting groups at high risk for disease as compared with focusing on the general population.
- To define risk assessment and discuss the role of epidemiology in risk assessment, including measurement of possible exposures.
- To appreciate how epidemiology can be used to shape public policy through the courts in the United States.
- To present how systematic reviews and meta-analysis as tools can be used to influence public policy and to consider how publication bias may affect the results of both systematic reviews and meta-analyses.
- To identify some possible sources of uncertainty in using the results of epidemiologic studies as a basis for making public policy.

A major role of epidemiology is to serve as a basis for developing policies that affect human health, including primary and secondary prevention and the optimal management of disease. As seen in previous chapters, the findings from epidemiologic studies may be relevant to issues in both clinical practice and community health and to population approaches to disease prevention and health promotion. As discussed in Chapter 1, the practical applications of epidemiology are often viewed as being so integral to the discipline that they are incorporated into the very definition of epidemiology. Historically, epidemiologic investigations were initiated to address emerging challenges relating to human disease (originally most often communicable diseases) and the health of the public. Indeed, one of the major sources of excitement in epidemiology is the direct applicability of its findings to alleviate problems of human health. This chapter presents an overview of some issues and problems relating to epidemiology in its application in formulating and evaluating public policy.

EPIDEMIOLOGY AND PREVENTION

The importance of epidemiology in prevention has been emphasized in several of the preceding chapters. Identifying populations at increased risk, ascertaining

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the cause(s) of their increased risk(s), and analyzing the costs and benefits of eliminating or reducing exposure to the causal factor or factors all require an understanding of basic epidemiologic concepts and of the possible interpretation of the findings of epidemiologic studies. In addition, assessing the strength of all available evidence and identifying any limits on the inferences derived or on the generalizability of the findings are critically important. Thus, epidemiology is often considered to be the "basic science" of prevention.

How much epidemiologic data do we need to justify a prevention campaign? Clearly, there is no simple answer to this question. Some of the issues involved differ depending on whether primary or secondary prevention is being considered. If we are discussing primary prevention, the answer depends on the severity of the condition, the costs involved (in terms of dollars, human suffering, and loss of quality of life if we do nothing out of the ordinary), the strength of the evidence implicating a certain causal factor or factors in the etiology of the disease in question, and the difficulty of reducing or eliminating exposure to that factor.

With secondary prevention, the issues are somewhat different. We must still consider the severity of the disease in question. In addition, however, we must ask whether we can detect the disease earlier than usual by screening and how invasive and expensive such detection would be. Additional considerations include whether a benefit accrues to a person who has the disease if treatment is initiated at an earlier-than-usual stage and whether there are harmful effects associated with screening. Epidemiology offers valuable approaches to resolve many of these issues.

In recent years considerable attention has been addressed to expanding what has been called the traditional risk-factor model of epidemiology, in which we explore the relationship of an independent factor (exposure) to a dependent factor (disease outcome) (Fig. 19.1). It has been suggested that this approach should be expanded in two ways: First, it should include measurement not only of the adverse outcome—the disease itself—but also of the economic, social, and psychological impacts resulting from the disease outcome on the individual, their family, and the wider community. Second, exposure to a putative causal agent is generally *not* distributed uniformly in a population. The factors that determine whether a person becomes exposed must therefore be explored if prevention is to be successful in reducing or preventing the exposure (Fig. 19.2). The full model is even more complex, as seen in Fig. 19.3: The relationship is influenced by *determinants of susceptibility* of the individual to the exposure; these include genetic factors together with environmental

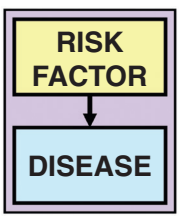

Fig. 19.1 Diagram of classic risk-factor epidemiology.

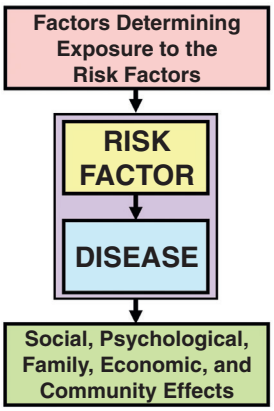

Fig. 19.2 Diagram of an expanded risk-factor epidemiology model to include determinants of exposure as well as social, psychological, family, economic, and community effects of the disease.

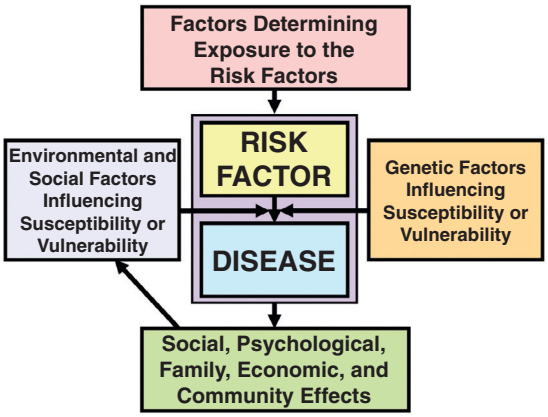

Fig. 19.3 Diagram of expanded risk-factor epidemiology model to include interrelationships of factors that determine susceptibility or vulnerability.

influences and social determinants, along with their possible interactions. Although such an expanded approach is intuitively attractive and provides an excellent framework in which to analyze public health problems, we still must demonstrate whether certain exposures or other independent variables are associated with increased risks of specific diseases.

In any case, deciding how much data and what types of data we need for prevention will be societally driven, reflecting society's values and priorities. Epidemiology, together with other public health disciplines, can provide much of the necessary scientific data that are relevant to addressing questions of risks and prevention. However, the final decision on initiating or sustaining a prevention program will be largely determined by local, regional or national economic and political considerations, as well as societal values. At the same time, it is hoped that such decisions will also be based on a firm foundation of scientific evidence provided by epidemiology and other relevant disciplines.

It is important to distinguish between *macroenvironmental* and *microenvironmental* exposures. Macroenvironmental exposures are exposures to things such as air pollution, which affect populations or entire communities. Microenvironmental exposures are environmental factors that affect a specific individual, such as diet (and the availability of healthy foods), smoking (by the individual or exposure to secondhand smoke), and alcohol consumption (personally and the availability of alcohol in the community). From the prevention standpoint, macroenvironmental factors are in many ways easier to control and modify, as this can be accomplished by legislation and regulation (e.g., setting environmental standards for pollutants). In contrast, modification of microenvironmental factors depends on modifying individual habits and lifestyle and addressing the availability of healthy food, green space, and safe neighborhoods, which can often be a much greater challenge.

In dealing with microenvironmental factors, providing scientific evidence and risk estimates is frequently not enough to induce individuals to modify their lifestyles (e.g., stopping smoking). Individuals often differ in the extent to which they are willing to take risks in many aspects of their lives, including health. In addition, the behaviors of individuals may differ depending on whether they are confronted with the risk of an adverse outcome or the probability of a positive event (Fig. 19.4).



Fig. 19.4 Risk of what? How the end point may affect an individual's perception of risk and willingness to act. (Steve Kelley. © 1998 San Diego Union Tribune. Copley News Service.)

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In addition, individuals often place the blame elsewhere for health problems brought on by their own lifestyles. Thus, risk communication, mentioned previously, must extend beyond communicating risk data to policy makers. It must also deal with communicating with the public in an understandable fashion in the context of people's perceptions of their risk, so that individuals will be motivated to accept responsibility and act on behalf of their own health to the greatest extent possible. Epidemiologists should work with health educators to more appropriately educate the public about personal risk issues, while acknowledging that human behavior change can be a major challenge.

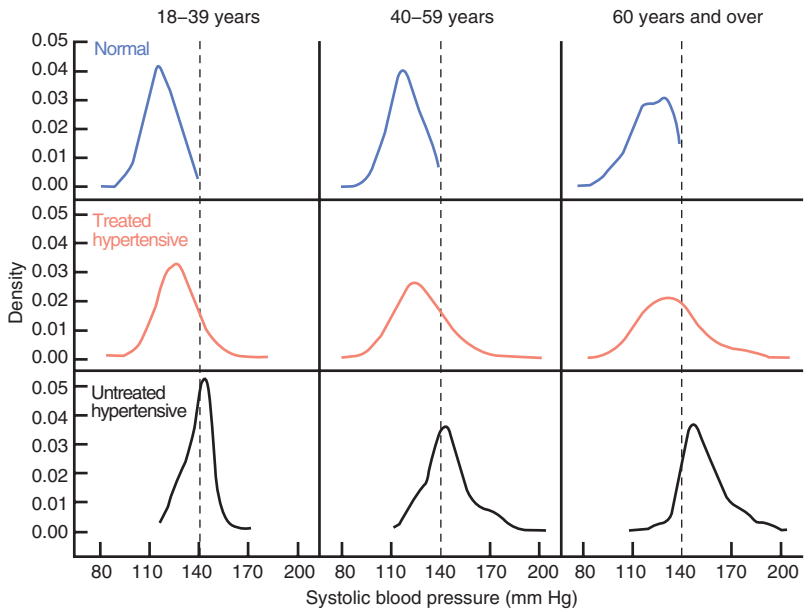
POPULATION APPROACHES VERSUS HIGH-RISK APPROACHES TO PREVENTION

An important question in prevention is whether our approach should target groups that are known to be at high risk or whether it should extend primary prevention efforts to the general population. This issue was first brought up by Geoffrey Rose in 1985[3] and later amplified by Paul Whelton in 1994[4] in a discussion of the prevention of hypertension as well as deaths from coronary heart disease (CHD).

Epidemiologic studies have demonstrated that the risk of death from CHD steadily increases with increases in both systolic and diastolic blood pressure; there is no known threshold. Fig. 19.5A and B shows the distribution of systolic blood pressures in the general population of men and women who are above 18 years of age in the United States (2001–2008), respectively.

Looking at the US general population above 50 years of age, Fig. 19.5C shows the risk of a composite end point of first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke in relation to systolic blood pressure—the risk increases steadily with higher levels of systolic blood pressure. Individuals below 60 years of age with systolic blood pressures of 160 mm Hg or higher had more than 1.50 times the risk of the composite CHD end point than those whose systolic blood pressure was below 140 mm Hg.

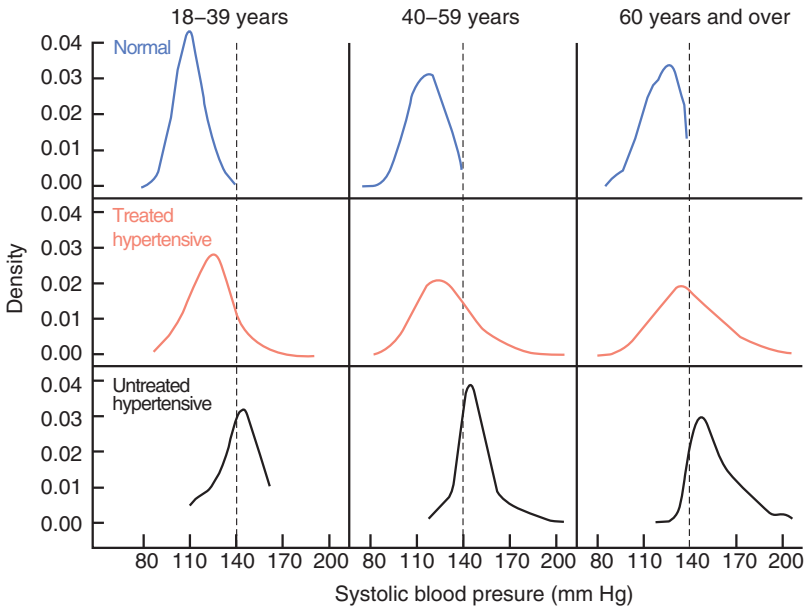
Based on the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High



NOTE: Vertical dashed rule is the systolic hypertension cutpoint.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2001–08.

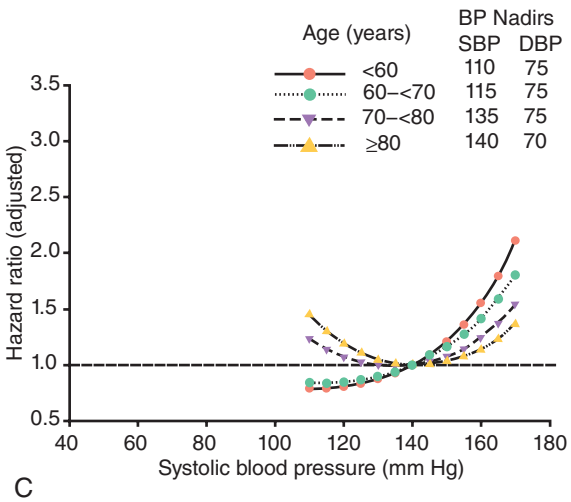
A

Fig. 19.5 **(A)** Mean systolic blood pressure for men aged 18 years and over, by age and hypertension status.



NOTE: Vertical dashed rule is the systolic hypertension cutpoint.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2001–08.

B



C

Fig. 19.5, cont'd **(B)** Mean systolic blood pressure for women aged 18 years and over, by age and hypertension status. **(C)** Adjusted hazard ratio of first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke as a function of age (in 10-year increments), systolic blood pressure *(SBP)*. Reference systolic blood pressure for hazard ratio: 140 mm Hg, respectively. Blood pressures *(BP)* are the on-treatment average of all postbaseline recordings. The quadratic terms for systolic blood pressures were statistically significant in all age groups (all $P < .001$). The adjustment was based on sex, race, history of myocardial infarction, heart failure, peripheral vascular disease, diabetes, stroke/transient ischemic attack, renal insufficiency, and smoking. *CDC,* Centers for Disease Control and Prevention; *DBP,* diastolic blood pressure; *NCHS,* National Center for Health Statistics. (A and B, From Wright JD, Hughes JP, Ostchega Y, et al. Mean systolic and diastolic blood pressure in adults aged 18 and over in the United States, 2001–2008. *Natl Health Stat Report.* 2011;[35]:1–22, 24. C, Modified from Denardo SJ, Gong Y, Nichols WW, et al. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *Am J Med.* 2010;123[8]:719–726.)

Blood Pressure (JNC 7), values as low as those defining prehypertension (systolic and diastolic blood pressures ranging from 120 to 139 mm Hg and 80 to 99 mm Hg, respectively) may result in a 20% excess risk of strokes.[5]

It therefore seems reasonable to combine a high risk focus within a population approach: one set of preventive measures addressed to those at particularly high risk and another designed for the primary prevention of hypertension addressing the general population.

Such analyses can have significant implications for prevention programs. The types of preventive measures that might be used for high-risk individuals often differ

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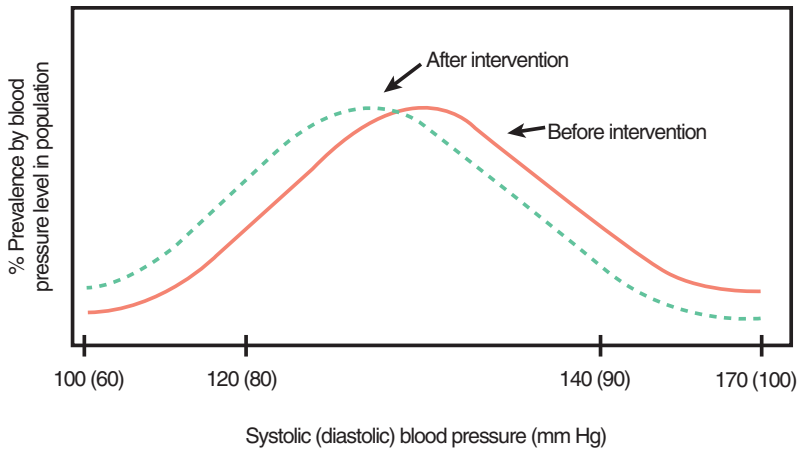


Fig. 19.6 Representation of the effects of a population-based intervention strategy on the distribution of blood pressure. (From National Institutes of Health. *Working Group Report on Primary Prevention of Hypertension*. NIH Publication No. 93–2669. Washington, DC: National Heart, Lung, and Blood Institute; 1993:8.)

from those that are applicable to the general population. Those who are at high risk and are aware that they are at high risk are more likely to tolerate more expensive, uncomfortable, and even more invasive procedures. However, in applying a preventive measure to a general population, the measure must be low cost and minimally invasive; it needs to be associated with relatively little pain or discomfort if it is to be acceptable to the general population. Seasonal influenza vaccination is one example of this prevention target, especially among the elderly. SARS-CoV-19 vaccination in the US was an example where, despite widespread availability of vaccination at no cost to the public, some 32% of the American population did not get vaccinated in 2020–2022.

Fig. 19.6 shows the goal of a population-based strategy, which is a downward shifting of the entire curve of blood pressure distribution when a blood pressure–lowering intervention is applied to an entire community, such as reduction of the salt content of processed foods. Because the blood pressure of most members of the population is above the very lowest levels that are considered optimal, even a small downward shift (shift to the left) in the curve is likely to have major public health benefits, as Rose suggested some four decades ago.[3] In fact, such a shift would prevent more strokes in the population than would successful treatment limited to "high-risk" individuals. Furthermore, Rose[3] pointed out that the high-risk strategy is essential to protecting susceptible individuals. Ultimately, however, our hope is to understand the basic cause of the incidence of a disease—in this case, elevated blood pressure—and to develop and implement the necessary means for its (primary) prevention. Rose concluded as follows:

> *Realistically, many diseases will long continue to call for both approaches, and fortunately competition between them is usually unnecessary. Nevertheless, the priority of concern should always be the discovery and control of the causes of incidence.*[3]

EPIDEMIOLOGY AND CLINICAL MEDICINE: HORMONE REPLACEMENT THERAPY IN POSTMENOPAUSAL WOMEN

Epidemiology can also be considered a basic science of clinical investigation. Data obtained from epidemiologic studies are essential in clinical decision making in many situations. An understanding of epidemiology is crucial to the process of designing meaningful studies of the natural history of disease, the quality of different diagnostic methods, and the effectiveness of clinical interventions. Epidemiology is highly relevant to addressing the many uncertainties and dilemmas in clinical policy, not all of which can easily be resolved.

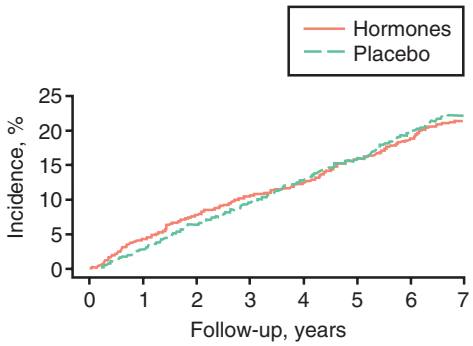
A dramatic example is the use of hormone replacement therapy (HRT) by postmenopausal women. In 1966 Robert Wilson, a physician, published a book titled

Feminine Forever, which advocated HRT for postmenopausal women. After the publication of this book, millions of postmenopausal women began taking estrogens in the hope of retaining their youth and attractiveness and avoiding the unpleasant, often encountered symptoms of menopause, such as hot flashes, night sweats, and vaginal dryness. The medical community largely accepted Wilson's recommendation for estrogen replacement, and even gynecology textbooks supported it. However, in the 1970s, an increased risk of uterine cancer was reported in women taking estrogen replacement. As a result, estrogen was subsequently combined with progestin, which counteracts the effect of estrogen on the uterine endometrial lining. This combination leads to monthly uterine bleeding that resembles a normal menstrual period.

Several nonrandomized observational studies subsequently appeared and reported other health benefits, such as fewer heart attacks and strokes, less osteoporosis, and fewer hip fractures associated with HRT. Considering the entire body of evidence that had accumulated, support for the conclusion that estrogen protected women against heart disease appeared strong and generally consistent. Women were advised that when they reached 50 years of age, they should discuss with their physicians whether they should begin HRT to protect themselves against heart disease and other conditions associated with aging.

Recognizing that there was little supporting evidence from randomized trials using hard disease end points, such as risk of myocardial infarction, two randomized trials were initiated: the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI). The HERS study[6] included 2,763 women with known CHD. It found that, in contrast to accepted beliefs, combination HRT *increased* women's risk of myocardial infarction during the initial years after starting therapy. The study failed to find evidence that HRT offered protection during a follow-up period of almost 7 years (Fig. 19.7).

The WHI[7] was a randomized, placebo-controlled trial of 16,608 women designed in 1991–1992 to evaluate HRT for the primary prevention of heart disease and other conditions common among older people. The planned duration of the trial was 8.5 years. One component (study arm) of the trial was a randomized, placebo-controlled investigation of estrogen plus progestin in postmenopausal women who had an intact uterus. This component of the study was stopped 3 years early because, by that time, results had shown increased risks of heart attack, stroke, breast cancer, and blood clots (Fig. 19.8). Although the study showed a reduced incidence of osteoporosis, bone fractures, and colorectal cancer, overall, the dangers from HRT outweighed the benefits.



No. at risk								
Hormones	1,380	1,303	1,247	1,196	1,133	1,043	984	354
Placebo	1,383	1,334	1,269	1,209	1,122	1,039	976	336

Fig. 19.7 Kaplan-Meier estimates of the cumulative incidence of coronary heart disease events (death and nonfatal myocardial infarctions). (From Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up [HERS II]. *JAMA*. 2002;288:49–57.)

Only about 2.5% of the enrolled women had adverse events. On the basis of the study results, it has been estimated that, annually, for every 10,000 women taking estrogen plus progestin, we would expect 7 more women to have a heart attack (37 women taking estrogen plus progestin would have a heart attack compared with 30 women taking placebo), 8 more women to have a stroke, 8 more women to have breast cancer, and 18 more women to have blood clots. At the same time, we would expect 6 fewer cases of colorectal cancer and 5 fewer hip fractures.

Many women who had been taking HRT were shocked by the results of the WHI. The findings strongly indicated that, in women taking estrogen plus progestin for protection against heart disease, the risks of cardiovascular end points were increased. These women were left uncertain as to whether to continue with HRT or whether to seek alternatives. Many also believed that they had been misled by the medical community because, for many years, they had been reassured about

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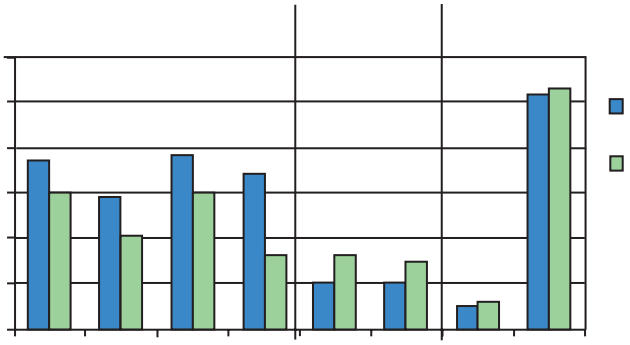

Fig. 19.8 Disease rates for women assigned to estrogen plus progestin or to placebo in the Women's Health Initiative (WHI) study. (WHI online. http://www.nhlbi.nih.gov/health/women/upd2002.htm. Accessed June 14, 2013.)

the effectiveness and safety of HRT by their physicians, *despite the absence of clear data* from placebo-controlled randomized trials. Complicating the decision-making process for women at the time of menopause is that the WHI did not address the question faced by many women who often take combination HRT for brief periods to prevent and relieve postmenopausal symptoms such as hot flashes.

A major methodologic question is why there was such a discrepancy between the results of the placebo-controlled randomized WHI study regarding risk of heart disease and the results of a large number of nonrandomized, observational studies that previously supported a protective benefit from combination HRT. This issue is of great importance because, in many areas of medicine and public health, we depend on the findings of nonrandomized, observational studies because the costs of randomized trials may be prohibitive, and randomized studies may not be feasible for other reasons (e.g., in the case of Pap smear screening for cervical cancer, the medical community had accepted the screening as necessary).

Several explanations have been offered.[8–10] In the observational studies, the women who were prescribed HRT were often healthier women who had a better cardiovascular risk profile. Women who use HRT are often better educated, leaner, more physically active, less likely to be smokers, more health-conscious, and of higher socioeconomic status than women who do not. Often, women who were prescribed HRT were judged to be compliant, and compliers often have other healthier patterns of behavior. Thus, confounding by lifestyle and other factors may have taken place in the observational studies. In addition, when adverse effects occurred early in the observational studies and led to the discontinuation of HRT, these events might not always have been identified in the periodic cross-sectional measurements used. An additional explanation related to cardiovascular risk is that the observational studies were conducted soon after menopause, when the beneficial effects of HRT—such as its favorable effects on lipids and endothelial function—are known to occur, whereas the WHI trial included much older women with extensive underlying atherosclerosis, among whom there is a predominance of the prothrombotic and inflammatory effects of HRT.[11]

Clearly in the future it will be essential to address these issues when nonrandomized observational studies are used as the basis for clinical guidelines development and dissemination and setting new public health policies.[12] Not discussed in this introductory textbook are attempts to make observational studies simulate randomized trials, including use of approaches such as instrumental variable and its genetic version, Mendelian randomization. However, application of these strategies requires certain assumptions that are difficult to meet[13]

EPIDEMIOLOGY AND REGULATORY DECISIONS: ANEMIA TREATMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Anemia is a common complication of chronic kidney disease (CKD). This is because the kidneys are the predominant source of erythropoietin, which in turn stimulates red cell production by the bone marrow. As CKD progresses anemia becomes more common. In 1989, epoeitin alfa was approved for the correction of anemia by the US Food and Drug Administration (FDA). Epoeitin alfa is a genetically engineered form of the human erythropoietin hormone. In 1998 and then subsequently in 2006, studies demonstrated that completely correcting anemia in hemodialysis and non-dialysis CKD patients, respectively, was associated with increased cardiovascular risk. The drug manufacturers pay doctors millions of dollars every year in return for prescribing this anemia medication, which led to extensive off-label use and the overutilization of erythropoietin stimulating agents (ESAs) in the United States (Fig. 19.9). In 1998 in the Normal Hematocrit trial,[14] published in the New England Journal of Medicine, raising the hematocrit in stable hemodialysis patients to normal levels was associated with an increased risk of death or myocardial infarction. The second trial, Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR),[15] in stable CKD patients, raising the hemoglobin to a higher target value of 13.5 g/dL was associated with an increased risk of death, myocardial infarction, hospitalization for congestive heart failure, and stroke, all without an improvement in quality of life as compared with a lower hemoglobin target of 11.3 g/dL (Fig. 19.10). In December of 2006, the Committee on Ways and Means of the US House of Representatives convened a hearing on patient safety and quality issues in end stage renal disease (ESRD) treatment. The lead first author of the CHOIR trial, Dr. Ajay Singh of Harvard Medical School, was asked to testify before the committee. Dr. Singh concluded his testimony[16] by "*I believe that the best recourse to try and prevent hemoglobin levels rising in both the dialysis population is to take the approach of bundling of services so that there is—we remove the financial incentives to use larger doses of EPO and aim for*

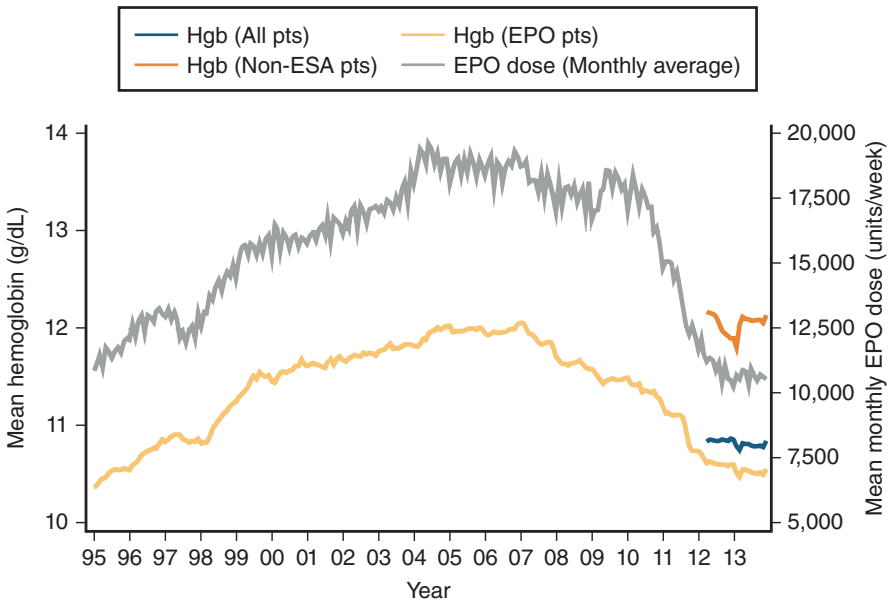

Fig. 19.9 Mean monthly hemoglobin *(Hgb)* level and mean monthly epoetin *(EPO)* dose (expressed as units per week) in adult hemodialysis patients on dialysis 90 days, Medicare claims, 1995–2013. *ESA,* Erythropoietin stimulating agent. (From US Renal Data System. 2015 USRDS annual data report volume 2: ESRD in the United States. https://www.usrds.org/2015/download/vol2_USRDS_ESRD_15.pdf. Accessed June 5, 2017.)

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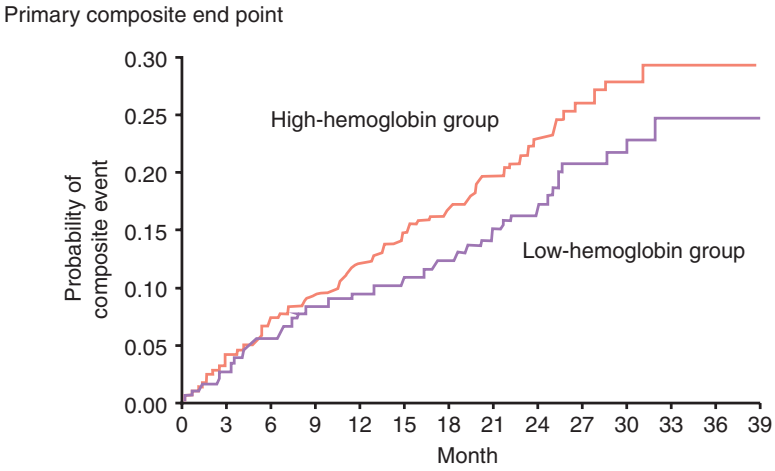

No. at Risk

High-hemoglobin	715	664	587	520	457	355	270	175	101	72	55	23
Low-hemoglobin	717	660	594	539	499	397	293	182	107	67	44	23

Fig. 19.10 Kaplan-Meier estimates of the probability of the primary composite end point (hospitalization for congestive heart failure without renal replacement therapy, myocardial infarction, stroke, and death). (From Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006;355:2085–2098.)

higher hemoglobin levels." As a result, in 2007, the US FDA issued a black box warning adding significant restrictions on the use of ESAs.[17] The black box warning includes the following: (1) prescribers should use the lowest dose of ESA that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid the need for red blood cell transfusion and (2) ESAs increase the risk for death and for serious cardiovascular events when administered to target a hemoglobin of greater than 12 g/dL.

EPIDEMIOLOGY AND PUBLIC HEALTH POLICY

In the wake of the COVID-19 pandemic, several guidelines and policies with varying degrees of enforcement were imposed around the world with the primary objective of minimizing the spread of infection of COVID-19, or "*flattening the [epidemic] curve*", which would reduce the pressure on healthcare systems in managing the influx of patients to the emergency departments and intensive care units in those who need mechanical ventilations, among other healthcare needs. In March/April 2020, multiple countries either completely closed their borders for incoming or outgoing flights, schools were closed, local jurisdictions ordered non-essential businesses to shut down, and for employees to go home and work remotely. Public health officials strongly recommended and local businesses and entities enforced wearing masks and social distancing. However, as it may not be practical to be shutdown forever, in the summer of 2020, public health officials recommended that communities may cautiously reopen in phases. This was coupled with a second wave of cases and deaths. As results from phase 3 trials of COVID-19 vaccines were being published, new hopes rose that a path to normality was at the end of the tunnel as authorities, businesses. and individuals encouraged vaccinations to their respective stakeholders. Nevertheless, a sizable percentage of the US population remained unvaccinated, especially young children.

RISK ASSESSMENT

A major use of epidemiology in relation to public policy is for risk assessment. Risk assessment has been defined as the characterization of the potential adverse health effects of human exposures to environmental

hazards. Risk assessment is thus viewed as part of an overall process that flows from research to risk assessment and then to risk management, as shown in Fig. 19.11. Samet and colleagues[18] reviewed the relationship of epidemiology to risk assessment and described risk management as involving the evaluation of alternative regulatory actions and the selection of the strategy to be applied. Risk management is followed by risk communication, which is the communication of the findings of the risk assessment to those who need to know the findings in order to participate in policy making and to take appropriate risk-management actions, including communications to the public at large.

The National Research Council (1983) listed four steps in the process of risk assessment[19]:

1. *Hazard identification:* Determination of whether a particular chemical is causally linked to particular health effects
2. *Dose-response assessment:* Determination of the relationship between the magnitude of exposure and the probability of occurrence of the health effects in question
3. *Exposure assessment:* Determination of the extent of human exposure before or after the application of regulatory controls
4. *Risk characterization:* Description of the nature—and often the magnitude—of human risk, including attendant uncertainty

Clearly epidemiologic data are essential in each of these steps, although epidemiology is not the only relevant scientific discipline in the process of risk assessment. Toxicology plays a major role as well, and an important challenge remains to reconcile epidemiologic and toxicologic data when findings from the respective disciplines disagree.

Several important methodologic problems affect the use of epidemiology in risk assessment. Because

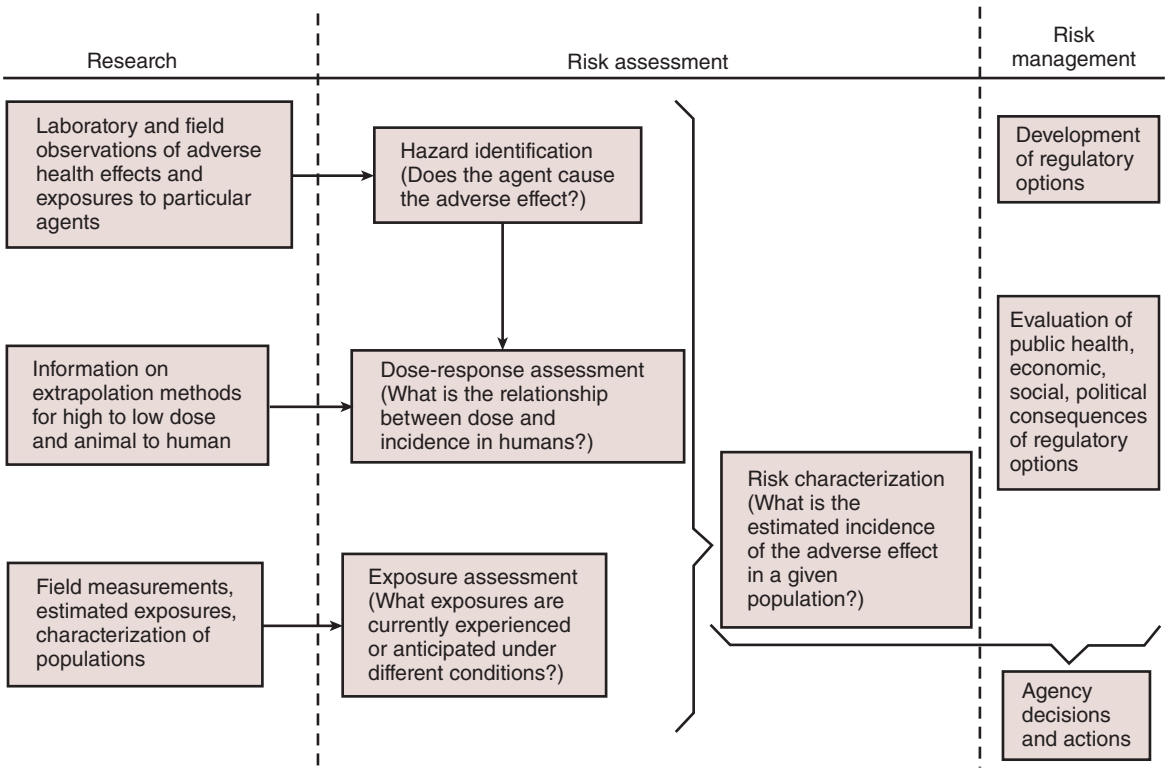

Fig. 19.11 Relationships among the four steps of risk assessment and between risk assessment and risk management. (Modified from Committee on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, National Research Council. *Risk Assessment in the Federal Government: Managing the Process*. Washington, DC: National Academy Press; 1983:21.)

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epidemiologic studies may address the relationship between an environmental exposure and the risk of a disease, rigorous assessment of each is critical. Perhaps the most significant problem is the assessment of exposures.

Assessment of Exposure

Data regarding exposure generally come from several types of sources (Box 19.1). Each type of source has advantages and disadvantages; the latter include lack of completeness and biases in reporting. Frequently investigators use several sources of information regarding exposure, but a problem often results when different sources yield conflicting information.

Another problem in exposure assessment is that macroenvironmental factors generally affect many individuals simultaneously, so that individual exposures may be difficult to measure. As a result, ecologic approaches are often chosen, in which aggregate rather than individual measurements are used (described in Chapter 7), and the aggregation is often carried out over large areas and populations. The characteristics of the community are therefore ascribed to the individuals residing in that community, but the validity of characterizing an individual exposure by this process is often open to question (recall the "ecological fallacy"). Furthermore, personal exposure histories can be quite difficult to obtain either retrospectively or prospectively and may be subject to considerable measurement error. The long latent or induction period between exposure and development of disease makes it necessary to ascertain long past exposures, which is particularly difficult and may be particularly subject to bias. Sometimes it is possible to evaluate exposure of macroenvironmental factors at the individual level, as was done in an ancillary study within the Multi-Ethnic Study of Atherosclerosis (MESA Air). In this study, household levels of air pollution were estimated by considering distance from a major roadway[20] and using a special device for the home monitoring of air pollution levels.[21]

BOX 19.1 Sources of Exposure Data

1. Interviews
   a. Subject
   b. Surrogate
2. Employment or other records
3. Physician records
4. Hospital records
5. Disease registry records (e.g., cancer registries)
6. Death certificates

A parallel set of problems is seen when we try to characterize the occupational exposures of an individual worker and to link an exposure at work to an adverse health outcome. First, because a worker is likely to be exposed to many different agents in an industrial setting, it is often difficult to isolate the independent risk that can be ascribed to a single specific exposure. Second, because there is often a long latent period between the exposure and the subsequent development of disease, studies of the exposure-disease relationship may be difficult; for example, unless a prospective study can be done (see Chapter 8), recall may be poor and records of exposure may have been lost. Third, increased disease risks may occur among those living near an industrial plant, so that it may be difficult to ascertain how much of a worker's risk results from living near the plant and how much is due to an occupational exposure in the work setting itself.

Perhaps the most fundamental problem in measuring exposures in epidemiologic studies is that sources and measures are often indirect. For example, considerable interest has arisen in recent years over the possible health effects of electromagnetic fields (EMFs). This interest followed the article of Wertheimer and Leeper in 1979,[22] which reported increased levels of leukemia in children living near high-voltage transmission lines. Subsequently, many methodologic questions were raised, and the question of whether such EMFs are associated with adverse health effects remains unresolved. For example, conclusions were discrepant in an update of two meta-analyses and a more recent meta-analysis done by the same first author![23,24]

In studying EMFs, several approaches are used for measuring exposure, including the wiring configuration in the home, spot or 24-hour measurements of the fields, or self-reports of electrical appliance use. However, the results of different studies regarding risk of disease differ depending on the type of exposure measurement used. In fact, actual EMF measurements, even 24-hour measurements, generate weaker associations with childhood leukemia than do those for wire configuration codes.[25] This observation raises a question about any possible causal link between exposure to magnetic fields and the occurrence of disease.

Even the best indirect measure of exposure often leaves critical questions unanswered. First, exposure is

generally not dichotomous; data are therefore needed regarding the *dose* of exposure to explore a possible dose-response relationship. Second, it is important to know whether the exposure was continuous or periodic. For example, in the pathogenesis of cancer, a periodic exposure with alternating exposure and non-exposure periods may allow for DNA repair during the non-exposure periods. In the case of a continuous exposure, no such repair can take place. Finally, information about latency is critical: How long is the latent period and what is its range? This knowledge is essential to focus efforts on ascertaining exposure during a particular time period in which a causal exposure might well have occurred.

Because of these problems in measuring exposure using indirect approaches, much interest has focused on the use of biologic markers of exposures. (Use of such biomarkers has often been termed *molecular epidemiology*.)[26] The advantage of using biomarkers is that they overcome some problems of limited recall or lack of awareness of exposures. In addition, biomarkers can overcome errors resulting from variation in individual absorption or metabolism by focusing on a later step in the causal chain.

Biomarkers can be markers of exposure, markers of biologic changes resulting from exposures, or markers of risk or susceptibility. Fig. 19.12 schematically represents the different types of exposures we may choose to measure.

We might also wish to measure ambient levels of possibly toxic substances in a general environment, the levels to which a specific individual is exposed, the amount of substance absorbed, or the amount of substance or metabolite of the absorbed substance that reaches the target tissue. Biomarkers bring us closer to being able to measure an exposure at a specific stage in the process by which an exposure is linked to human disease. For example, we can measure not only environmental levels of a substance but also DNA adducts that reflect the effect of the substance on biologic processes in the body after absorption.

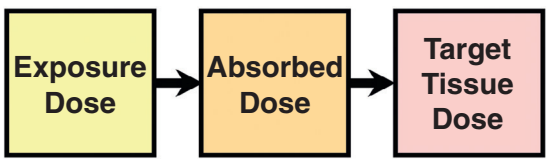

Fig. 19.12 What exposures are we trying to measure?

Nevertheless, despite these advantages, biomarkers generally give us a dichotomous answer—a person was either exposed or not exposed. Biomarkers generally do not shed light on several important questions, such as the following:

- What was the total exposure dose?
- What was the duration of exposure?
- How long ago did the exposure occur?
- Was the exposure continuous or periodic?

An example of some of these shortcomings is salivary cotinine, which is a biomarker of nicotine absorption in smokers. As it is a marker only for recent (past 3 days) smoking, it does not provide information on duration of exposure or whether the habit was continuous or periodic.

The answers to these questions are crucial in properly interpreting the potential biologic importance of a given exposure. For example, in assessing the biologic plausibility of a causal inference being made from observations of exposure and outcome, we need relevant data that will permit us to determine whether the interval observed between the exposure and the development of the disease is (biologically) consistent with what we know from other studies about the incubation period of the disease.

In addition to these concerns, a potential limitation of the use of exposure biomarkers is that, in a traditional case-control study, collection of a biologic sample and measurement of a biomarker are done only after the onset of the disease. Thus, it is impossible to find out whether the exposure was present prior to the onset of the disease of interest. This shortcoming, however, is not present in case-control studies within a cohort in which biologic samples, such as serum or urine, are frozen and stored at baseline—that is, before incident cases develop during follow-up of the cohort.

Use of biomarkers is not new in epidemiology. Even before the revolution in molecular biology, laboratory techniques were essential in many epidemiologic studies; these included bacterial isolates and cultures, phage typing of organisms, viral isolation, serologic studies, and assays of cholesterol lipoprotein fractions. With the tremendous advances made in molecular biology, a new variety of biomarkers has become available that is relevant to areas such as carcinogenesis. These biomarkers not only identify exposed individuals but also cast new light on the pathogenetic process of the disease in question.

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SYSTEMATIC REVIEWS AND META-ANALYSES

While discussion of systematic reviews and meta-analyses are discussed in detail in Chapter 11, we will present here their applications as relevant to public and health policy.

First, several scientific questions arise when epidemiologic data are used for formulating public policy:

1. Should epidemiologic methods that detect small increases in risk be considered clinically meaningful?
2. How can we reconcile inconsistencies between animal models and human data?
3. How can we use incomplete or equivocal epidemiologic data?
4. How can results be interpreted when the findings of epidemiologic studies are inconsistent?

Many of the risks with which we are dealing may be quite small, but they may potentially be of great public health importance because of the large numbers of people exposed, with a resulting potential for adverse health effects in many people (recall the hypothesis proposed by Rose[3]). However, an observed small increase in relative risk above 1.0 may easily result from bias or from other methodologic limitations, and such results must therefore be interpreted with great caution unless the results have been replicated and other supporting evidence has been obtained.

Given that the results of different epidemiologic studies may not be consistent and that at times they may be in dramatic conflict, attempts have been made to systematize the process of reviewing the epidemiologic literature on a given topic. One process, the systematic review, uses standardized methodology to select and assess peer-reviewed articles to synthesize the literature regarding a specific health topic.[27] Systematic reviews may be accompanied by a process called meta-analysis, which has been defined as "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings."[28] Recall that meta-analysis allows for aggregating the results of a set of studies included in a systematic review, with appropriate weighting of each study for the number of subjects sampled and for other characteristics. It can help to give an overall perspective on an issue when the results of studies disagree.

However, several problems and questions are associated with meta-analysis. First, should the analysis include all available reports (for example, presentations at scientific meetings or pre-print postings) or only studies published in the peer-reviewed literature? Second, when the relative risks or odds ratios from various studies differ (i.e., the results are not homogeneous), meta-analysis results may mask important differences among individual studies. It is therefore essential that a systematic review resulting in a meta-analysis include only studies that meet well-established design and quality criteria. Third, the results of meta-analyses themselves may not always be reproducible by other analysts. Finally, a systematic review with or without meta-analysis is subject to the problem of publication bias (discussed later in this chapter). Fig. 19.13 shows a hypothetical "forest plot" and the definition of its components. The forest plot is the type of presentation that is frequently used to show the results of individual studies as well as the results of the meta-analysis. Fig. 19.14 shows a forest plot on the relationship of socioeconomic status and depression. Note that of the 51 studies included in this meta-analysis, 5 suggest a negative association. Thus, the results of this meta-analysis are not entirely homogeneous.

Meta-analysis was originally applied to randomized trials, but this technique is now being more commonly used increasingly to aggregate nonrandomized, observational studies, including case-control and cohort studies. In these instances, the studies do not necessarily share a common research design. Hence the question arises as to how similar such studies need to be in order to legitimately be included in a meta-analysis. In addition, appropriate control of biases (such as selection bias and misclassification bias) is essential but often proves to be a formidable challenge in meta-analyses.

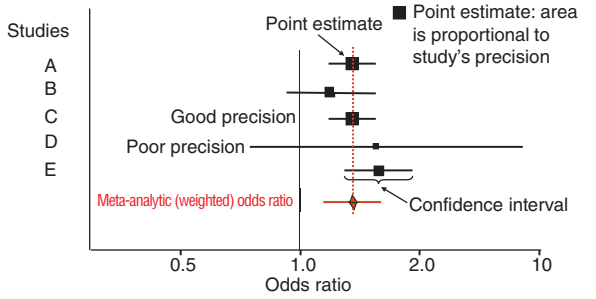

Fig. 19.13 Hypothetical forest plot, with components, labeled, showing the type of diagrammatic presentation frequently used to show results of individual studies *(A–E)* as well as the results of a meta-analysis.

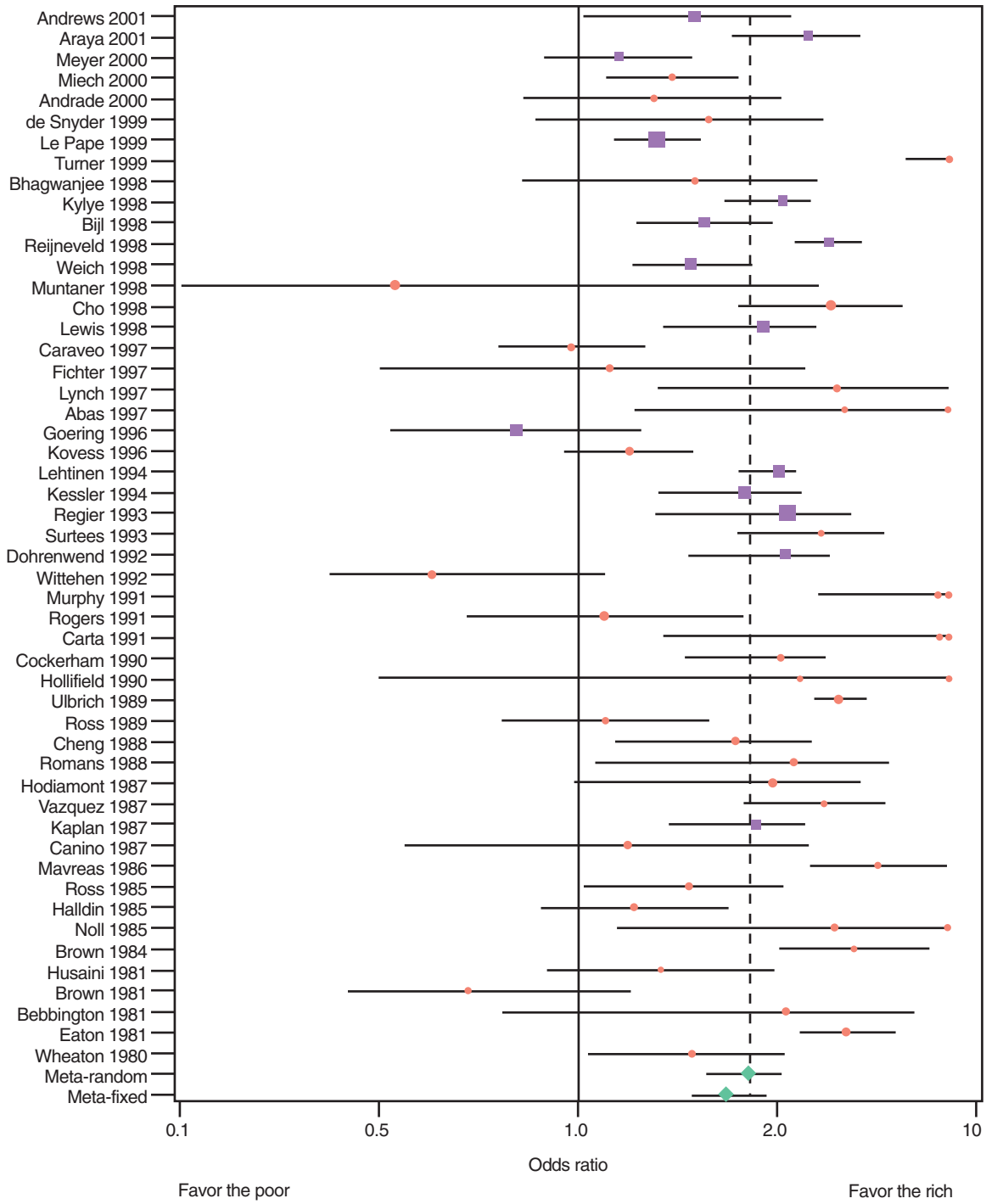

Fig. 19.14 Odds ratios for major depression in the lowest socioeconomic status group in 51 prevalence studies published after 1979. *Horizontal lines,* 95% confidence interval. Squares show original estimates; diamonds show meta-analyzed results. (From Lorant V, Deliège D, Eaton W, et al. Socioeconomic inequalities in depression: a meta-analysis. *Am J Epidemiol.* 2003;157[2]:98–112.)

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In view of the considerations just discussed, meta-analysis remains a subject of some controversy.

A final problem with meta-analysis is that in the face of all the difficulties discussed, putting a quantitative imprint on the estimation of a single relative risk or odds ratio from all the studies may lead to a false sense of certainty regarding the magnitude of the risk. People often tend to have an inordinate belief in the validity of findings when a number is attached to them; as a result, many of the difficulties that arise in meta-analysis may at times be ignored.

PUBLICATION BIAS

Chapter 16 discussed the use of twin studies as a means of distinguishing the contributions of environmental and genetic factors to the root cause of disease. In that discussion it was mentioned that the degree of concordance and discordance in twins is an important observation for drawing conclusions about the role of genetic factors, but that estimates of concordance reported in the literature may be inflated by publication bias, which is the tendency for articles to be published that report concordance for rare diseases in twin pairs.

Publication bias is not limited to genetic studies of twins; it can occur in any area of epidemiology. It is a particularly important phenomenon in the publication of articles regarding environmental risks and on the results of clinical trials. Publication bias may occur because investigators do not submit the results of their studies when the findings do not support "positive" associations and increased risks (that is, "null findings"). In addition, journals may differentially select for publication studies that they believe to be of greatest reader interest, and they may not find studies that report no association to fall in this category. As a result, a literature review that is limited to published articles may preferentially identify studies that report increased risk. Clearly such a review is highly selective in nature and omits many studies that have obtained what have been called "negative" results (i.e., results showing no effect), which may not have reached publication. In addition, since 2020, there has been an increased use of pre-print online servers. These are online repositories of research articles in which authors can upload their manuscripts without peer-review with the primary purpose of making their findings quickly available for decision makers and their scientific colleagues without potential lengthy delays from peer-review process. This approach may have helped expedite the availability of some evidence at the beginning of COVID-19 when we did not know much about it. Given the lack of peer-review of articles in preprint servers, the quality and credibility of such manuscripts cannot often be determined.

Publication bias therefore has a clear effect on systematic review and meta-analysis. One approach to this problem is to try to identify unpublished studies and to include them in the analysis (pulling studies from the "gray" literature, often from conference presentations, often reporting null results, that do not lead to publication). However, the difficulty here is that, in general, unpublished studies are likely not to have passed journal peer review; therefore their suitability for inclusion in a meta-analysis may be questionable. Regardless of whether we are discussing a traditional type of literature review or a structured meta-analysis, the problem of potential publication bias must be considered.

It has been proposed that in order to prevent publication bias in systematic reviews (and thus, in meta-analyses), study registers, like the Cochrane collaboration, should be implemented. There are also strategies to evaluate publication bias in meta-analyses, including the Beggs funnel and tests of symmetry. These approaches are based on plotting the studies' values of the measure of association (e.g., relative risk or odds ratio) against their precision levels (measured by their standard errors, which are usually a function of their sample sizes). Using the relative risk as an example, as the standard errors increase, thus denoting decreasing precision, the relative risks become more variable, but it is expected that they follow a symmetric distribution around the between-study mean relative risk. If the distribution is asymmetric, publication bias is likely.

EPIDEMIOLOGY IN THE COURTS

As mentioned earlier, litigation has become a major path for policy making in the United States. Epidemiology is assuming ever-increasing importance in the legal arena. Particularly in the area of toxic torts, it provides one of the major types of scientific evidence that is relevant to the questions involved. Issues such as effects of dioxin, silicone breast implants, tobacco smoking, and EMFs are but a few examples of how epidemiologic evidence is used in court cases.

However, the use of data from epidemiologic studies is not without its problems. Epidemiology answers questions about *groups*, whereas the court often requires information about *individuals* (where it is necessary to causally link individual exposure and their disease status). Furthermore, considerable attention has been directed to the court's interpretation of evidence of causality. Whereas the legal criterion is often "more likely than not"—that is, that the substance or exposure in question is "more likely than not" to have caused a person's disease—epidemiology relies to a great extent on the US Surgeon General's guidelines for causal inferences.[29] It has been suggested that an attributable risk in the exposed greater than 50% might constitute evidence of "more likely than not."[30]

Until recently, evidence from epidemiology was only reluctantly accepted in the courts, but this has changed to a point where epidemiologic data are often cited as the only source of relevant evidence in toxic tort cases. For many years the guiding principle for using scientific evidence in the courts in the United States was the Frye test, which states that for a study to be admissible, "it must be sufficiently established to have gained general acceptance in the field in which it belongs."[31] Although terms such as "general acceptance" and "field in which it belongs" were left undefined, it did lead to an assessment of whether the scientific opinion expressed by an expert witness was generally accepted by other professionals in the discipline.

In 1993, in *Daubert v. Merrell Dow Pharmaceuticals*,[32] a case in which the plaintiff alleged that a limb deformity at birth was due to ingestion of the drug Bendectin during pregnancy, the US Supreme Court articulated a major change in the rules of evidence. The court ruled that "general acceptance" is not a necessary condition for the admissibility of scientific evidence in court. Rather, the trial judge is now considered a "gatekeeper" and is assigned the task of ensuring that an expert's testimony rests on a reliable foundation and is relevant to the "task at hand." Thus, the judge "must make a preliminary assessment of whether the testimony's underlying reasoning or methodology is scientifically valid and can be properly applied to the facts at issue." Among the considerations cited by the court are whether the theory or technique in question can be and has been tested and whether the methodology has been subjected to peer review and publication.

Given their new responsibilities, judges presiding at trials in which epidemiology is a major source of evidence must have a basic knowledge of epidemiologic concepts—including, for example, study design, biases and confounding, and causal inference—if they are to be able to rule in a sound fashion on whether the approach used by the experts follows accepted "scientific method." Recognizing this need, the Federal Judicial Center has published the *Research Manual on Scientific Evidence* for judges, which includes a section on epidemiology.[33] Although it is premature to know the ultimate effect of the Daubert ruling, given the tremendous increase in the use of epidemiology in the courts, it will clearly require enhanced knowledge of epidemiology by many parties involved in legal proceedings that use evidence derived from epidemiologic studies.

A more contemporary example on the use of epidemiologic evidence in the courts is the legal challenges that occurred during the COVID-19 pandemic in the US. Several lawsuits have been brought to the US judicial system related to various topics to challenge public health measures, e.g., school closures, mask mandates, COVID vaccinations etc. The court system will have to analyze and synthesize the epidemiologic evidence, or lack thereof, that is presented before the court on these issues to make its decision. On the other side, some employees sued their employers for negligence in not providing a safe working environment during the COVID-19 pandemic. In such cases, the court will use evidence from multidisciplinary sciences of medicine, public health, occupational medicine, and industrial hygiene, to make a decision.[34]

SOURCES AND IMPACT OF UNCERTAINTY

In 1983, the National Research Council in the United States wrote:

> *The dominant analytic difficulty [in conducting risk assessments for policy decision making] is pervasive uncertainty ... data may be incomplete, and there is often great uncertainty in estimates of the types, probability, and magnitude of health effects associated with a chemical agent, of the economic effects of a proposed regulatory action, and of the extent of current and possible future human exposures.*[35]

This insight remains as relevant today as when it was originally written 40 years ago. Uncertainty is a reality that we must accept and that must be addressed. Uncertainty is an integral to science. What we believe to be "truth" today often turns out to be transient. Tomorrow

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a study may appear that contradicts or invalidates the best scientific information available to us today.

Uncertainty is relevant not only to risk assessments but also to issues of treatment, to issues of prevention such as screening, and to health economics issues. Clearly it is a relevant concern in the legal setting discussed earlier (Fig. 19.15).

Some of the possible sources of uncertainty are listed in Box 19.2. The sources of uncertainty may be in the design of the study or in the conduct and implementation of the study, or they may result from the presentation and interpretation of the study findings. Many of these sources are addressed in earlier chapters.



"Your Honor, we, the jury, find this one too close to call."

Fig. 19.15 One jury's approach to uncertainty. (Arnie Levin/The New Yorker Collection/The Cartoon Bank.)

One issue listed in Box 19.2 is whether, in a study of the effectiveness of a preventive measure, the results are described as a relative risk reduction or an absolute risk reduction. Often the *percent* reduction in mortality is selected because it gives a more optimistic view of the effectiveness of a preventive measure. If, however, absolute risk reduction is used, such as the *number* of individuals per 1,000 whose lives would be saved, the result appears less impressive (recall the disease risks associated with HRT presented earlier in this chapter). If the rate of adverse events, such as mortality from the disease that is observed without screening, is low, a percent reduction will always seem more impressive than an absolute risk reduction because the *number* of events that could potentially be prevented is small even if the *percent* reduction is higher. If, for example, the mortality in those screened is 1 per 100,000 and in those not screened is 2 per 100,000, the reduction resulting from screening is 50%, but the absolute difference is merely 1 per 100,000.

A more relevant measure of the effectiveness (and efficiency) of a preventive or curative measure is the

BOX 19.2 Examples of Possible Sources of Uncertainty in Epidemiology

1. Uncertainty resulting from the design of the study
   - a. The study may not have been designed to provide a relevant answer to the question of interest
   - b. Biases that were not recognized or not adequately addressed
     - (1) Selection bias
     - (2) Information bias
   - c. Measurement errors, which may lead to misclassification
   - d. Inadequate sample size
   - e. Inappropriate choice of analytic methods
   - f. Failure to take into account potential confounders
   - g. Use of surrogate measures that may not correctly measure the outcomes that are the major dependent variables of interest
   - h. Problems of external validity (generalizability to the population of interest): the conclusions regarding potential interventions may not be generalizable to the target population
2. Uncertainty resulting from deficiencies in the conduct and implementation of the study
   - a. Observations may be biased if observers were not masked
   - b. Poor quality of laboratory or survey methods
   - c. Large proportion of nonparticipants and/or nonrespondents
   - d. Failure to identify reasons for nonresponse and characteristics of nonrespondents
3. Uncertainty resulting from the presentation and interpretation of the study findings
   - a. How were the results expressed?
   - b. If the study assessed risk and possible etiology, were the factors involved described as risk factors or causal factors?
   - c. If the study assessed the effectiveness of a proposed preventive measure, was the benefit of the measure expressed as relative risk reduction or absolute risk reduction? Why was it chosen to be expressed as it was, and how was the finding interpreted?

number needed to undergo the intervention to prevent one case or one death from the disease. This measure is based on the absolute difference. For example, if the difference between a new preventive strategy and the current (standard of care) strategy is 20%, the number needed to have the intervention in order to prevent the occurrence of one incident case is $([100 \times 1] \div 20) = 5$. However, if the difference is only 2%, this number becomes $([100 \times 1] \div 5) = 20$. Note that the effectiveness is the same if the mortality rates are, for example, 60% and 40% or 6% and 4% in two studies evaluating different novel interventions to prevent the same disease: $([60\% - 40\%] \div 60\%) = 33.3\%$ in the first study, and $([6\% - 4\%] \div 6\%) = 33.3\%$ in the second study. It is, however, clear that the first study deals with a far more important public health problem for which prevention would be more efficient, as one case can be prevented by subjecting fewer individuals to the new approach.

Another issue that contributes to uncertainty in policy making that is not generally related to specific epidemiologic studies is how we deal with *anecdotal evidence,* such as that provided by a person who states that she was screened for breast cancer 10 years earlier, received early treatment, and is alive and apparently well 10 years after the screening. There is often a tendency to accept such evidence as supporting the effectiveness of the screening in reducing mortality from the disease. However, anecdotal evidence has two major problems. First, it does not consider slow-growing tumors that might have been detected by screening but might not have affected survival even if the patient had not been screened. Second, it does not consider very fast-growing tumors that screening would have missed, so that the person would not have received early treatment. For those giving anecdotal evidence of survival after screening, there is no comparison group of individuals who were screened but did *not* survive. As an unknown sage has said, "The plural of *anecdote* is not 'data.' " Nevertheless, despite these major limitations, anecdotal evidence given by patients who have survived serious illnesses may have a strong emotional impact, which may significantly influence policy makers.

Ultimately the impact of scientific uncertainty on the formulation of public policy will depend on how the major stakeholders consider uncertainty. Among the different groups of stakeholders are scientists (including epidemiologists), policy makers, politicians, and the public (or the target populations). Each of these groups may have a different level of sophistication, a different level and type of self-interest, and may view data differently and be influenced to varying degrees by colleagues, friends, and various constituencies in society. Moreover, individuals have different personalities with different levels of risk tolerance and different ways of dealing with uncertainty. An important mediator is the set of values that every individual has relating to issues such as the value of a human life and the principles that should guide the allocation of limited resources in a society. The result is a complex interaction of uncertainty, resulting from characteristics of a study, interacting with a network of relationships relating to the elements just described. A schematic of some of the interrelationships influencing the effect of uncertainty on public policy is shown in Fig. 19.16. These factors are clearly major concerns in formulating appropriate public health and clinical policy. It is important that they be considered if a plan of action is to be successfully developed and implemented to address health issues in the population.

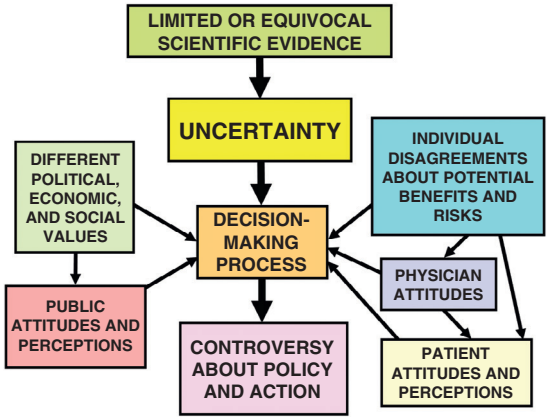

Fig. 19.16 Schematic presentation of some of the factors involved in the impact of uncertainty on the decision-making process for health policy.

POLICY ISSUES REGARDING RISK: WHAT SHOULD THE OBJECTIVES BE?

Public policy is generally recognized to be largely developed through the processes of legislation and regulation. As discussed earlier, in the United States, litigation has also become an important instrument for developing and implementing public policy. Ideally, each of these processes should reflect societal values and aspirations.

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Certain major societal issues must be considered in making decisions about risk. Among the questions that must be confronted are the following:

1. What percentage of the population should be protected by the policy?
2. What level of risk is society willing to tolerate?
3. What level of control of risk is society willing to pay for?
4. Who should make decisions about risk?

At first glance, it might seem appealing to protect the entire population from any amount of risk, but realistically this is difficult if not impossible to accomplish. Regardless of what we learn from risk data about populations, there are clearly rare individuals who are extraordinarily sensitive to minute concentrations of certain chemicals. If the permissible amount of a chemical is to be set at a level that protects *every* worker, it is possible that entire manufacturing processes might have to be halted. Similarly, if we demand zero risk for workers or for others who may be exposed, the economic base of many communities might be destroyed. Policy making therefore requires a balance between what *can* be done and what *should* be done. The degree of priority attached to elimination of all risk and the decision as to what percentage of risk should be eliminated (or conversely, tolerated) clearly are not scientific decisions but rather depend on societal values. It is hoped that such societal decisions will capitalize on available epidemiologic and other scientific knowledge in the context of political, economic, ethical, and social considerations.

CONCLUSION

The objectives of epidemiology are to enhance our understanding of the biology, pathogenesis, and other determinants of disease to improve human health and to prevent and better treat disease. A thorough understanding of the methodologic issues that arise is needed to better interpret epidemiologic results properly as a basis for formulating both clinical and public health policy. The appropriate and judicious use of the results of epidemiologic studies is fundamental to an assessment of risk to human health and to the control of these risks. Such use is therefore important to both primary and secondary prevention. Policy makers are often obliged to develop policy in the presence of incomplete or equivocal scientific data. In clinical medicine, in both the diagnostic and therapeutic processes, decisions are often made with incomplete or equivocal data; this has perhaps been more of an overt impediment in public health and community medicine. No simple set of rules can eliminate this difficulty. As H. L. Mencken wrote: "*There is always an easy solution to every human problem—neat, plausible, and wrong.*"[36] A major challenge remains to develop the best process for formulating rational policies under such circumstances—a process that is relevant for both clinical medicine and public health.

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20

Ethical and Professional Issues in Epidemiology

No man is an Island, entire of itself;
every man is a piece of the Continent, a part of the main ...
any man's death diminishes me, because I am involved in Mankind;
And therefore never send to know for whom the bell tolls;
It tolls for thee.

—John Donne, English clergyman and poet (1572–1631), Meditation XVII

LEARNING OBJECTIVES

- To discuss the ethical obligations that investigators have to people who volunteer to participate in epidemiologic studies.
- To consider how the privacy and confidentiality of health records is protected in epidemiologic studies and how access to epidemiologic data is governed.
- To describe the scientific and ethical implications of classifying race and ethnicity in epidemiologic studies.
- To introduce issues associated with conflict of interest.
- To review how the findings of epidemiologic studies are interpreted and communicated to the public.

In the lines cited at the beginning of this chapter, John Donne emphasizes the interconnectedness of all people. Epidemiology also teaches us major lessons about connections and relationships. The previous chapters have demonstrated that disease does not arise in a vacuum. Many contagious diseases clearly depend on human (and frequently animal) contacts for transmission and for the propagation of epidemics. Moreover, in recent years, more and more diseases that for a long period were thought not to have an infectious etiology are being identified as being of infectious origin to varying degrees. For example, the microorganism *Helicobacter pylori* has been implicated in the etiology of peptic ulcer and gastric cancer (see Chapter 14). Virtually all cases of cancer of the cervix are linked to human papillomavirus (HPV), especially types 16 and 18; the foundation thus exists for promoting prevention programs through immunization against HPV among youth for lifelong prevention.

A major focus of epidemiology is on the impact of the environment on the risk of human disease. This reflects a combination of factors: First, we are at risk from effects of nature, including flooding and other natural disasters, such as the tsunami that affected Japan in 2011, causing massive damage at the Fukushima Daiichi Nuclear Power Plant; Hurricane Maria in 2017, which devastated Puerto Rico and the US Virgin Islands; and the earthquake in Mexico City, which killed some 2000 inhabitants in 2017. Second, we are also vulnerable to the environmental and ecologic damage resulting from certain human attitudes, lifestyles, and behaviors. The negative effects that human activities have on our planet are often not adequately considered, and some influential decision makers are in abject denial of their existence. These activities and effects include air pollution, depletion of the ozone layer, global warming, climate change, the pollution of natural water supplies and deforestation among many others. The negative effects of many of these types of problems are only now beginning to be fully understood and appreciated, with the legacy of environmental damage being left to future generations. As these problems are studied, increased understanding is also needed of individual

variations in genetically determined human vulnerability to environmental agents.

Another aspect of interdependence that is relevant to epidemiologists is their need to develop collaborative relationships with other epidemiologists, as well as with professionals in other fields. We have learned that many epidemiologic investigations require multidisciplinary approaches; that is, professionally, epidemiologists cannot be most productive and effective as "islands." Thus, the lesson of "connectedness" expressed in John Donne's lines seems integral both to the dynamics of the diseases and conditions investigated by epidemiologists and to the everyday practice of epidemiology. It also applies to the participation of epidemiologists in formulating and implementing health-related policy, as demonstrated by the story of Semmelweis presented in Chapter 1.

Today, we live in a depersonalized era in which individuals often consider their own advancement to be life's major goal. A sense of community and concern for others is often lost. John Donne's worldview, stressing people's interdependence, at times seems alien to some current views of the world, one of which is humorously seen in Fig. 20.1. One of the best articulations of the need to simultaneously balance the competing interests and needs of the individual and the community was given by Hillel, a Talmudic sage who lived some 2,000 years ago. He said: "If I am not for myself [If I don't take care of myself], who will be for me? But if I am only for myself [in other words, if I take care only of myself], what am I worth? And if not now, when?"

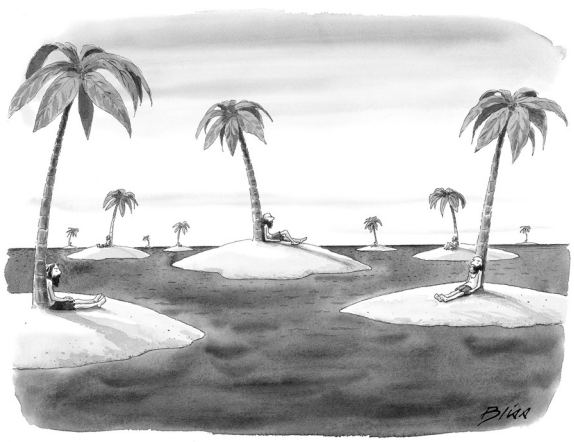

Fig. 20.1 "No man is an island"—a different view. (Harry Bliss/The New Yorker Collection/The Cartoon Bank.)

Another factor that has an impact on epidemiology and epidemiologists is the rapid pace of societal change and technologic progress. A story is told of Adam and Eve in the Garden of Eden. After being expelled from Eden, Adam turned to Eve and said, "*Eve, my dear, we are living in a time of change*."[1] In the 21st century, we too are living in a time of dramatic change. The rapidly evolving social and scientific context in which epidemiologic research is being conducted has led to new challenges for those working in epidemiology, for those who use the results of epidemiologic studies, and for the general public. In addition, major technologic advances, including tremendous increases in computing capacity and dramatic advances in laboratory technology (for example, recall Chapter 16 on the significant advances in genetics in the past several years), have made it possible to rapidly analyze large numbers of biologic samples and maintain enormous data sets. These advances have made possible many population-based studies that would not have been conceivable even a decade or two ago. The electronic medical record (EMR) is replacing paper charts in hospitals and includes outpatient and inpatient visits, results of laboratory tests, electrocardiography (ECG) readings, and computed tomography/magnetic resonance imaging (CT/MRI) scans. How to use these data (which have not been collected for research purposes) for epidemiologic studies is a major challenge to "big data" analysis. At the same time, these technologic advances have introduced new and different issues related to privacy, confidentiality, and the individual. Furthermore, the emergence of the COVID-19 pandemic and the unprecedented advancements in screening, vaccines, and therapeutics have led to significant societal and policy changes.

In light of the preceding discussion, this chapter briefly reviews some ethical and professional issues that are critical for epidemiologic research and for applying the results of this research to the improvement of human health. The issues to be discussed include several that relate to the actual conduct of epidemiologic studies and others that relate to broader societal issues and go beyond actual epidemiologic research itself.

ETHICAL ISSUES IN EPIDEMIOLOGY

Clearly, in any scientific pursuit, fraud, deceit, or misrepresentation elicits universal disapproval and condemnation from members of the discipline, other professionals,

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and the lay public. Such issues are not presented in this chapter. Today some of the most difficult ethical dilemmas in epidemiology are likely to be more subtle, involving judgments, philosophies, attitudes, and opinions for which consensus may be more difficult to obtain.

Does epidemiology differ from other scientific and medical disciplines with regard to ethical issues? Although epidemiology shares many characteristics with other scientific disciplines, it differs in some important ways. It is a discipline that largely grew out of public health and medicine, and even in its earliest years, its findings had immediate policy implications for public health action or clinical care. John Snow's studies of cholera in London (see Chapter 1) and his removal of the handle from the Broad Street pump, which his studies had implicated in the cholera outbreak (whether the pump handle was actually removed before or after the peak of the outbreak), reflected the clear policy implications of his findings.

The ultimate objective of epidemiology is to improve human health; epidemiology is a basic science of disease prevention. Hence the relationship of epidemiology to the development of public policy is integral to the discipline. As a result, the ethical and professional issues go beyond those that might apply to a scientific discipline, such as biophysics or physiology, and must be viewed in a broader context. First, epidemiologic findings have direct and often immediate societal relevance. Second, epidemiologic studies are generally funded from public resources and often have major implications for the allocation of limited societal resources. Third, epidemiologic research often involves human subjects in some way, and subjects who participate in epidemiologic studies generally derive no personal benefit from participating in these studies or from the study results.

INVESTIGATORS' OBLIGATIONS TO STUDY SUBJECTS

What are the investigators' obligations to the subjects in the nonrandomized observational studies with which most epidemiologists generally deal? First, to the greatest extent possible, a truly informed consent consistent with the principle of individual autonomy should be obtained from every subject. But can a truly informed consent be obtained from a subject in an epidemiologic study? If we believe that a full disclosure to the subjects of the study's objectives and hypotheses will introduce a response bias or other type of bias, clearly the consent cannot be a fully "informed" one. Another issue in consent relates to privacy and confidentiality. For many years, in good conscience, epidemiologists assured subjects that their data would be kept confidential, and that this commitment was unqualified. However, research data have become subject to court subpoena in recent years, with only a few exceptions. Therefore, the assurance of confidentiality given in informed consent statements must now include qualifications to allow for breaches in confidentiality that could be legally mandated and that would therefore be beyond the control of the investigator. Privacy regulations went into effect in the United States in 2003, which significantly affect the rights of patients regarding health information (Fig. 20.2). We all too often hear about data breaches and the release of confidential information that can be used to harm research participants or cause damage to their reputations and bank accounts or that involve other types of fraud. We return to the subject of privacy and confidentiality later in this chapter.

Another issue pertains to balancing the rights of the individual and the welfare of society. In a very early study of men at high risk for infection with the human immunodeficiency virus (HIV), the participants were given an assurance of confidentiality. In the baseline interview that was subsequently administered, subjects were asked whether they had donated blood during the previous 2 years. Several subjects who were found to be HIV-positive reported having given blood within the 2 years prior to the HIV testing. The concern that emerged was that the donated blood might have been used in a transfusion. Although the blood may have been discarded by the blood bank, there was no way to check on this without breaching confidentiality and violating the original commitment to the subjects. Perhaps the investigators should have anticipated such a problem at the time the interview was developed, before obtaining the subjects' informed consent. But even with foresight, these types of problems arise. In this case, how do we balance the original commitment to the subjects with a need to determine whether anyone had received blood from these donors, so that further transmission of HIV might be prevented?

A third obligation to the subjects relates to communicating the results of the study to them at the study's completion. Our approach to this issue may differ depending on whether the subject has been found to

OMB # 0920-0950

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

CONSENT/ASSENT AND PARENTAL PERMISSION FOR EXAMINATION AT THE MOBILE EXAMINATION CENTER

Print name of participant _____ _____ _____

First Middle Last

PARENT OR GUARDIAN OF SURVEY PARTICIPANT WHO IS UNDER 18 YEARS OLD:
For the Parent or Guardian of the Survey Participant who is a minor (unless the participant is an emancipated minor)

I have read the Examination Brochure and the Health Measurements List, which explain the nature and purpose of the survey. I freely choose to let my child take part in the survey.

_____ _____
Signature of parent/guardian Date

FOR PARENT OR GUARDIAN OF SURVEY PARTICIPANT 12-17 YEARS:

☐ I agree to have my child's interview about his/her current health status, diet, and health behaviors recorded for quality control.

☐ I do not agree to have my child's interview about his/her current health status, diet, and health behaviors recorded for quality control.

SURVEY PARTICIPANT WHO IS 12 YEARS OLD OR OLDER:

I have read the Examination Brochure and the Health Measurements List, which explain the nature and purpose of the survey. I freely choose to take part in the survey.

_____ _____
Signature of participant Date

If you are 18 and older and do not want a written report of your exam results, check here ☐

I observed the interviewer read this form to the person named above and he/she agreed to participate by signing or marking this form.

_____ _____
Witness (if required) Date

Name of staff member present when this form was signed: _____

Assurance of Confidentiality: We take your privacy very seriously. All information that relates to or describes identifiable characteristics of individuals, a practice, or an establishment will be used only for statistical purposes. NCHS staff, contractors, and agents will not disclose or release responses in identifiable form without the consent of the individual or establishment in accordance with section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)) and the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA, Title 5 of Public Law 107-347). In accordance with CIPSEA, every NCHS employee, contractor, and agent has taken an oath and is subject to a jail term of up to five years, a fine of up to $250,000, or both if he or she willfully discloses ANY identifiable information about you. In addition, NCHS complies with the Federal Cybersecurity Act of 2015 (6 U.S.C. §§ 151 & 151 note). This law requires the federal government to protect federal computer networks by using computer security programs to identify cybersecurity risks like hacking, internet attacks, and other security weaknesses. If information sent through government networks triggers a cyber threat indicator, the information may be intercepted and reviewed for cyber threats by computer network experts working for, or on behalf of, the government.
02/2017

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SP ID

Fig. 20.2 Sample consent form. (National Health and Nutrition Examination Survey [NHANES] Consent/Assent and Parental Permission for Examination at the Mobile Examination Center. Retrieved from Centers for Disease Control and Prevention https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/documents/2017_adult_consent_form.pdf. Accessed November 2, 2018.)

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have developed a health problem linked to an exposure being studied or whether the subject has only been found to be at increased risk for future development of disease as a result of exposure. In either case, clearly and concisely communicating the results regarding risk to the subjects can be viewed as one possible expression of the *ethical principle of beneficence*—the obligation of the investigator to help the subjects further their important legitimate interests, such as disease prevention and control, for themselves and for their families and friends. However, according to this principle, we must not only provide the benefits such as prevention of disease but also balance the benefits and costs or harm *(principle of utility)*.

If, for example, a subject has been exposed to a factor that is shown in a study to be a strong marker of the subclinical phase of a malignant neoplasm, should the subject be given this information? On the one hand, given that no effective treatment for that neoplasm is available and that there is no strong evidence that early detection of the disease is beneficial, might we be increasing a person's anxieties by transmitting this information without providing any benefit to that person?

On the other hand, we could argue that a participant in any study is entitled to receive the findings of the study even if the findings have no direct bearing on the person's health or even if they may lead to heightened anxiety. Why should we as investigators make this decision for participants? Indeed, many epidemiologists now offer all participating subjects the option of requesting a report of the study findings when the study has been completed.

PROTECTING PRIVACY AND CONFIDENTIALITY

Concerns about privacy and confidentiality in our society have increased with the increasing erosion of individual privacy through computerized records. Protection of privacy and confidentiality within the framework of medical investigation, including epidemiologic research, has become an important issue. The origins of such concerns are quite old. Hippocrates wrote in the now commonly used Oath of Physicians:

> *that whatsoever I shall see or hear ... of the lives of men and women ... which is not fitting to be spoken ... I will keep inviolably secret.*

As Hippocrates qualified "whatsoever I shall see or hear" with the phrase "which is not fitting to be spoken," he apparently considered certain types of information to be of a nature that *is* "fitting to be spoken." Presumably, under certain circumstances, Hippocrates would have advocated the carefully monitored sharing of personal information in the interest of societal benefit. For example, if a case of smallpox was diagnosed in an American city, Hippocrates would probably support reporting this case to health authorities. Thus, individual autonomy regarding privacy and confidentiality is an important principle, but it is not unlimited.

In regard to privacy and confidentiality in epidemiologic studies, attention has focused on the use of medical records (both paper charts, in the past, and the EMR more commonly today). Let us ask why medical records are needed in epidemiologic studies. These records are needed for two main purposes: (1) to generate aggregate data or validate information obtained by other means without having to contact patients and/or (2) to identify individual patients for subsequent follow up using means such as interviews or laboratory tests.

Because epidemiology's objectives of improving human health are clearly laudable, one might be tempted at first glance to dismiss any concerns about misuse of medical record data and about intrusions into individual privacy by epidemiologists. However, the words of Supreme Court Justice Louis D. Brandeis ring as true today as when they were first written in 1928:

> *Experience should teach us to be most on guard to protect liberty when the Government's purposes are beneficent. Men born to freedom are naturally alert to repel invasion of their liberty by evil-minded rulers. The greatest dangers to liberty lurk in insidious encroachment by men of zeal, well-meaning but without understanding.*[2]

The *ethical principle of autonomy* argues strongly for a meaningful informed consent in many areas related to research, including privacy and confidentiality. Concerns about protection of confidentiality in the research arena are valid. Over the years, these concerns have led to two major legislative proposals that look reasonable at first but in actuality would seriously damage epidemiologic research and impede progress in both public health and clinical practice. The two proposals are as follows:

1. Patient consent should be required before investigators are allowed access to medical records.

2. Data from medical records should be made available to investigators without any information that would identify an individual.

Both proposals are consistent with the ethical principle of *nonmaleficence*—doing no harm—to the subjects participating in a research study. However, if society has a vested interest in the findings from epidemiologic and other biomedical studies, it is necessary to strike a balance between the interests of the individual and those of the community at large.

Let us consider each of these two proposals separately. Why would the first proposal, which requires patient consent before investigators are allowed access to medical records, make many studies impossible?

- As a first step in a study, records must often be reviewed to identify which patients meet the study criteria for recruitment (for example, which patients have the disease in question and are therefore eligible for inclusion in a case-control study).
- Many epidemiologic studies are conceived only many years after a patient has been hospitalized (e.g., a new test may have become available that was not in use when the patient became ill), so informed consent could not have been obtained from the patient at that time. By the time the study is later developed, which could be years or decades later, many patients may have died or may no longer be traceable.
- Certain patients refuse to be interviewed in epidemiologic studies, but the nonparticipants can be characterized using data in their medical records, so that any biases resulting from their nonparticipation can be assessed. If records were not available because of patient refusals, a potential selection bias would then be introduced, and its magnitude and direction could not be assessed.

Turning to the second proposal, why is information from medical records that identifies individual patients essential for most epidemiologic studies?

- Reviewing medical records is often the first step in identifying a large enough group of persons with a disease who could then be followed up.
- Identifying information is essential for linking the records of specific individuals from different sources (such as hospital records, physicians' records, employment records, and death certificates, as in studies of occupational cancer).

As seen in Fig. 20.3, linkage of records is critical for generating unbiased and complete information about each subject, not only in occupational studies (as shown here) but also in many types of epidemiologic investigations. An example is a nonconcurrent cohort study (see Chapter 8) to evaluate the relationship of estrogen receptor status in breast cancer to mortality by using data from medical records and conducting linkage with the National Death Index.

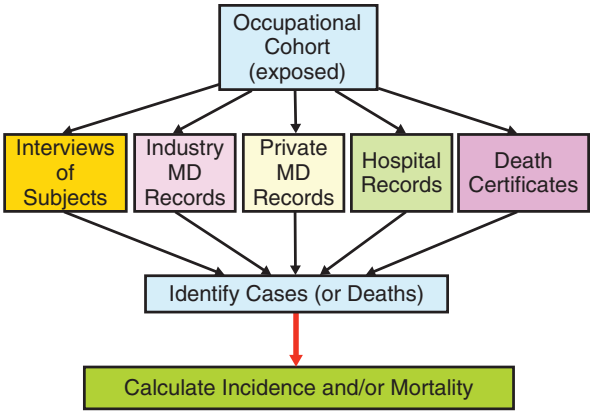

Fig. 20.3 Use of record linkage in occupational studies.

Thus, we see that the use of medical records is frequently essential for epidemiologic studies. Indeed, many significant advances in protecting human health that resulted from epidemiologic research could not have been made if access to medical records had been restricted.[3] At the same time, however, we must be concerned about protecting individual privacy and confidentiality. For many years, epidemiologic studies have used the following procedures designed to protect the confidentiality of subjects:

- Informed consent is required from study participants for all phases of research except review of medical records. The informed consent language must be consistent with the educational level of the participants (generally set at an eighth-grade comprehension level).
- All data obtained are stored under lock and key.
- Only study numbers are used on data forms; no personal identifiers are available on data forms or in computer files. Analysts are provided only with deidentified data for analysis. The key for linking study numbers with individual names is kept separately under lock and key by the principal investigator or his or her proxy (study coordinator).

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- Individual identifying information is destroyed at the end of the study unless there is a specific justification for retaining this information. Such retention must be approved by the institutional review board (IRB) or committee on human research.
- All results are published only in aggregate or group form so that individuals are never identified.
- Unless it is essential for the study, individual identifying information is not entered in computer files, and individual identifiers (such as small-area geographic locations) are not included in routine tabulations generated from computerized data.
- The importance of maintaining privacy and confidentiality is regularly emphasized to the research staff.

When people consent to participate in epidemiologic studies, they have voluntarily agreed to some invasion of their privacy for the common good of society, hoping for advances in health promotion and disease prevention as a result of the studies they are making possible. Therefore investigators have an ethical obligation to protect the privacy and confidentiality of the subjects in these studies to the greatest extent possible. The policies described earlier that are currently in force have been highly successful in achieving this goal.

Recognizing the importance of the use of medical records in epidemiologic research and the effectiveness of current measures to protect privacy and confidentiality, the Privacy Protection Study Commission recommended that patient consent not be required for the use of medical records in epidemiologic research.[4] However, the picture changed dramatically in the United States when federal privacy regulations went into effect pursuant to the Health Insurance Portability and Accountability Act of 1996 (HIPAA).[5] The act was introduced in response to increasing public concern about lack of individual control over medical information and the general erosion of individual privacy in the United States. Electronic transfer of medical information and fears about potential misuse of genetic information made available by new laboratory methods also led to the development of these new regulations.

The HIPAA regulations provided the first systematic nationwide privacy protection for health information in the United States. The regulations give patients more control over their health information and set boundaries for the use and release of health records. With some exceptions, signed authorization is now required from each individual for the release of his or her protected health information. Protected health information can be disclosed to public health authorities without individual authorization for public health purposes, including (but not limited to) public health surveillance, investigations, and interventions. Protected health information can also be released for health research without individual authorization under certain conditions, including the following: (1) if an IRB has provided a waiver, (2) for activities preparatory to initiation of research, and (3) for research on a decedent's information.[6] Extensive discussions of the regulations have been published.[7–9]

ACCESS TO DATA

When a study has been completed, who "owns" the data? Who should have access to the data—either "raw" or partially "cooked"—and under what conditions? We live in an era in which we can be confident that virtually any research data generated that deal with a controversial issue will be reanalyzed by real or alleged experts who support different positions. Some of the relevant questions regarding sharing of data include the following:

- At what point has a study truly been completed?
- Should the policy on sharing research data be dependent on who has paid for the study?
- Should the policy depend on who is requesting the data and on that person's possible motivations in making the request?
- Under what conditions should identifiers of individual participants be included with the data? Generally, data sharing requires removing all individual identifiers from the data, some of which may be subtle, such as for example identification of race/ethnicity of an individual in a city where only a very small percentage of individuals of a given race/ethnicity live.
- How can the investigator's interests be protected?
- Can all of the data be accessed or are only summary data made available?
- How extensive should data sharing be—should it be limited to requested variables or must the entire data set be shared?
- Can anyone request the data, or are the data restricted?
- Who will pay for the expenses involved in sharing data?

The challenge is to strike an appropriate balance between the interests of the investigator on the one hand and those of society on the other, for they do not inevitably coincide.

RACE AND ETHNICITY IN EPIDEMIOLOGIC STUDIES

An important issue that has received increasing attention in recent years is the use of race and ethnicity designations in epidemiologic studies. These variables are used both to describe populations and to test hypotheses in which race may serve as an independent variable, as in the many epidemiologic studies on racial disparities in health status. A PubMed review of the search terms *race, ethnicity, health* in October 2017 generated 17,603 publications and *race ethnicity disparities* yielded 12,001 records. Clearly race and ethnicity are the focus of many medical and epidemiologic investigations. However, there is concern about the use of these terms in epidemiologic research.

In an important paper published in 2008, Jay Kaufman and Richard Cooper discuss the concept of race as used in epidemiology and propose a set of cautions in its use. Race and ethnicity cannot be treated as dichotomous variables, as "human variation is continuous, not discrete," and ultimately, "existing racial classification schemes are the result of historical and political processes and that there is nothing natural, objective, or scientific about them."[10]

As a descriptor, race is often used to characterize the individuals who are studied in clinical trials or to describe inclusions and exclusions of populations in different types of epidemiologic studies. Race and ethnicity used as this type of variable can be helpful for this purpose and may be important for assessing the potential generalizability of the findings beyond the population studied.

When variables that designate race or ethnicity are included in studies designed to test hypotheses, the focus is often on possible associations of race with certain health outcomes. However, as Bhopal and Donaldson[11] have pointed out, biologically, race is ill defined, poorly understood, and may be of questionable validity. DNA research indicates that genetic diversity is a continuum with no clear breaks that can delineate racial groups.[12] Race has been described as "an arbitrary system of visual classification" that does not demarcate distinct subgroups of the human population.[13] Beginning with the 2000 US census, new guidelines permit respondents to identify themselves with more than one racial group. In the future, this policy may complicate the use of census data on race in epidemiologic studies.

An alternate approach is to use ethnicity rather than race. However, classifying people by ethnicity is also not simple or straightforward. Ethnicity is a complex variable that implies shared origins or social backgrounds; shared culture and traditions that are distinctive, maintained between generations, leading to a sense of identity and group; or shared language or religious tradition.[14] What have been the results of using racial designations in epidemiologic research? Many believe that, given the ambiguities involved in defining race, research using disease rates according to race has not significantly advanced our fundamental understanding of the causes and pathogenesis of human disease.[15] However, some have argued that even if such designations have not enhanced our understanding of the biologic mechanisms of disease, the use of racial variables in research has helped to identify subgroups—particularly minority and immigrant groups—to whom additional health care resources need to be directed. For example, race-specific mortality data in the United States have shown that[16]:

- A Black infant is more than twice as likely as a White infant to die in the first year of life.
- Black people are more likely to have end-stage renal disease but less likely to receive kidney transplants than White people.
- Black individuals are more likely to develop hypertension.
- Death rates for most causes of death are much higher for Black people than for White people.

In studies of the health needs and health care priorities of various populations, the race of a population group may be described, an explicit comparison may be made with other racial and ethnic groups, or a comparison may be implied but not explicitly stated. Death rates by race are frequently used for setting national and state health objectives. The Centers for Disease Control and Prevention state that, "death rates by race and Hispanic origin are important for monitoring the health status of these population groups and for informing policies and programs directed to reducing disparities."[16]

One problem in using racial variables is that in so doing, even well-meaning investigators may inadvertently

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stigmatize certain population subgroups. As a result, certain racial designations may, in effect, become surrogates for undesirable lifestyle characteristics such as criminal behavior and drug abuse. As Bhopal has pointed out, "by emphasizing the negative aspects of the health of ethnic minority groups, research may have damaged their social standing and deflected attention from their health priorities."[15]

What conclusions can we draw? No variable, including race, should be included uncritically as a matter of routine in any epidemiologic study. Perhaps the best approach in planning any epidemiologic study in which race will be addressed is to ask a number of questions, including the following:

- Why is race being studied?
- On what basis will study participants be classified by race?
- How valid will the designations of race be, and how will they contribute to increasing our biologic knowledge of the disease in question or to enhancing preventive activities in certain disadvantaged groups?

If race is being used as a surrogate for certain lifestyle factors, such as diet, could information on diet or other lifestyle factors be obtained directly, without using race as a surrogate?

- At the same time, we should also ask whether any damage may be done by using racial designations in a given study and whether such designations may unintentionally serve as virtual surrogates for undesirable lifestyles or characteristics.
- Is the construct validity of certain variables the same across races or ethnicities? For example, education is often used as a proxy for socioeconomic status (SES). Does education express SES to the same extent in Black people and White people in the United States?

In any study, racial variables that are used should have a definite purpose that can be precisely articulated and should meet the same standards of reliability and validity that we would expect of any other variables we measure in our study. The potential benefit of using such variables in a study should clearly exceed any potential harm that may result. Race may be an appropriate and potentially valuable variable to address in epidemiologic studies, provided the above issues have been adequately considered and addressed.

Jean-Claude Moubarac conducted a comprehensive review of the use of race and ethnicity in reports on health disparities in epidemiology and public health.[17] He presented a review of 280 articles published between 2009 and 2011 and identified four major remaining issues. First, researchers generally failed to differentiate race from ethnicity. Second, authors frequently ascribed ethnicity from racial categories. Third, common measurement procedures underlying each concept were rarely specified clearly. And fourth, there was a general failure to ascribe limits to the race and ethnicity taxonomies commonly used. Thus, it is clear that far greater precision is needed if race and ethnicity are to be appropriately investigated in epidemiology in the future.

CONFLICT OF INTEREST

Both actual and perceived biases may result from conflict of interest. Such conflict can arise at each stage of a study, from an initial decision as to whether a specific study should be undertaken in the first place through analysis and interpretation of the data and dissemination of the results. Epidemiologic investigation in the United States today is performed by epidemiologists who work in academia, industry, and government. These three environments differ in several ways. Funding for epidemiologic research in government and industry is generally internal, whereas academic epidemiologists must seek external financial support from government, industry, or foundations. As a result, research performed by academic epidemiologists is generally subjected to more rigorous peer review as part of the grant application process. Even more important, however, is that the employer of the academic epidemiologist generally has no vested interest in what the results of the study turn out to be. This contrasts with other settings in which the employer may be significantly affected—politically, economically, or legally—by the nature of the research findings. Consequently, overt or subtle pressure by an employer not to initiate a study or to prolong the process leading to reporting of the results (or their suppression) can introduce a serious bias into reviews of the literature concerning issues such as occupational hazards. Moreover, these biases may be impossible to assess.

The potential bias resulting from such studies that have not been conducted and that might well have revealed associations of specific exposures with adverse outcomes has not been named. In this context, some may be reminded of a dialogue in Sir Arthur Conan Doyle's Sherlock Holmes story *Silver Blaze* in which

Holmes investigates the disappearance of a racehorse with that name and the murder of its trainer. As Holmes is about to leave the village during the investigation, the local inspector turns to him and asks:

> *"Is there any point to which you wish to draw my attention?"*
>
> *"To the curious incident of the dog in the night time." [replies Holmes]*
>
> *"The dog did nothing in the night time."*
>
> *"That was the curious incident," remarked Sherlock Holmes.*[18]

(Holmes later described how he successfully identified the villain. He explained that when the intruder entered the stable "the dog did nothing in the night time" and did not even bark much, indicating that "obviously, the midnight visitor was someone whom the dog knew well.")

With this conversation in mind, the potential bias introduced by studies that are not done might be called *Silver Blaze bias.* Holmes understood why the dog failed to act and was able to apply this knowledge to solve the problem at hand. Similarly, there may be much to learn when a manufacturer fails to conduct what seems to be a clearly needed study of possible adverse effects of a product. But when such an association has been suggested, it is often difficult to determine whether certain epidemiologic studies were not initiated because of vested interests and concerns about the potential results of the study. In the absence of evidence documenting an explicit decision not to conduct a certain study, this type of bias is often difficult or impossible to quantify or even detect.

Although academic settings are not immune to their own problems and pressures, problems relating to epidemiologic research that arise in an academic setting are less likely to be linked to the potential impact of the study's specific findings. Nevertheless, the possibility of conflict of interest relating to any epidemiologic study must be considered, regardless of the specific setting in which the research was conducted. Indeed, such conflict may be related more to sources of funding than to the research setting itself. However, the possibility must be recognized that, infrequently, institutional as well as individual conflicts of interest may influence the publication and dissemination of results. Efforts should be expended to ensure that, to avoid publication bias, the results of the study—whatever they may turn out to be—are published in a peer-reviewed journal in a timely fashion. Requirements for registering clinical trials are a major step in that direction (see discussion in Chapter 11). Sponsorship of the study should be clearly acknowledged in the article that reports the results of the study, as should any financial or other interests of the investigators or their families that may be affected by the study results.

Note that sometimes even if there is no real conflict of interest, there may be an appearance of a conflict, which must also be dealt with.

INTERPRETING FINDINGS

Many critical issues regarding how epidemiologic studies are conducted arise in connection with the appropriateness of the study design and with the interpretation and reporting of findings. Epidemiologists are often accused of endlessly reporting new risks, many of which are not large and are not confirmed in subsequent studies. The public finds many reported but often unconfirmed risks in the media, which leads them to become skeptical of newly reported risks because they are unable to sort out true and important risks from unconfirmed or trivial ones (Fig. 20.4); they frequently then become unwilling to take responsibility for their own health care if the facts are in doubt.[19] The question again arises: How do we assess the importance of a single study that shows an increased risk? How many confirmatory studies are needed?

An additional problem is that in earlier years, initial solitary epidemiologic findings or scientific controversies were generally addressed and often resolved within the scientific community before findings were disseminated to the public. Today, both initial unconfirmed reports and scientific controversies are often aired in the press or in the popular media (and increasingly in social media) even before the studies have appeared in peer-reviewed journals (Fig. 20.5). The dilemma is that although enhanced public education and increased public awareness of scientific issues are laudable, anxiety levels are often unjustifiably raised by single studies that are widely reported and often later refuted. The problem is exacerbated by a reported bias in newspapers against reporting the results of studies that show no effect.[20] In June 2020, a new paper was published by Joyner et al. that reported safety data on the use of convalescent plasma in 20,000 hospitalized

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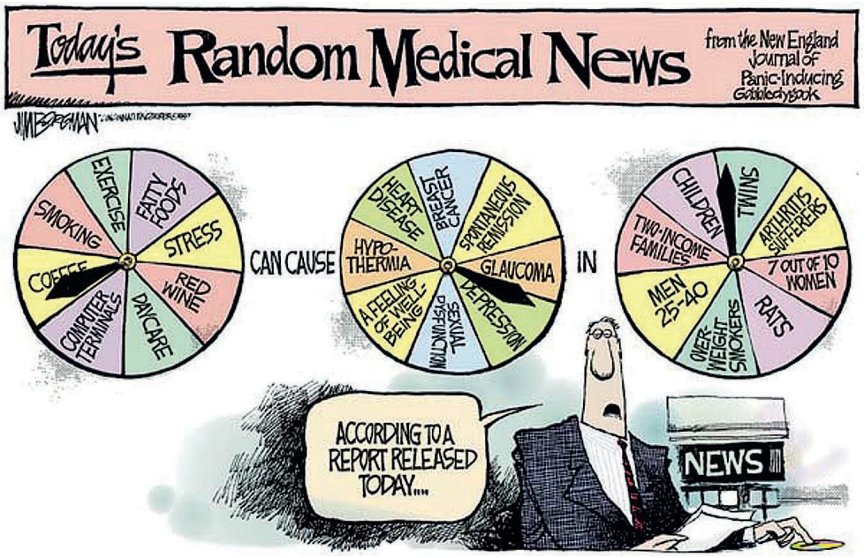

Fig. 20.4 One view of the seemingly endless stream of reported risks confronting the public. (© James Borgman—USA TODAY NETWORK)



Fig. 20.5 Dealing with scientific uncertainty. (Mischa Richter/The New Yorker Collection/The Cartoon Bank.)

patients with COVID-19.[21] The authors analyzed data from the US Food and Drug Administration Expanded Access Program for COVID-19, in which all patients in the dataset were exposed to convalescent plasma. Shortly thereafter, this article was cited in the news as a justification for recommending the use of convalescent plasma in hospitalized COVID-19 patients, touting the "robust safety data" from this paper. The authors concluded "*These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality*". A letter to the editor by Farag[22] was published in the same journal in which he reported limitations of this analysis that hindered any strong conclusion made

in the paper. Farag detailed various design, analytic, and interpretation flaws of the study. To name a few, the authors never reported the timing of the administration of convalescent plasma, there was no comparison group of hospitalized COVID-19 patients, and the incidence rates of adverse events and mortality were not adjusted for known confounders. The authors, however, inappropriately attributed the temporal decline of COVID-19 mortality to administration of convalescent plasma, notwithstanding the fact that the CDC provided data showing that the declining mortality resulted from the fact that younger and healthier individuals had relatively lower risk of COVID-19-related mortality compared with older individuals with preexisting comorbid conditions. While later evidence may have shown some potential efficacy of use of convalescent plasma in hospitalized COVID-19 patients, the prior conclusion made by Joyner et al. was inappropriate.

Significant uncertainty is associated with the findings regarding certain questions, such as whether mammography is beneficial for women in their 40s and whether prostate-specific antigen testing is beneficial to men with non-invasive prostate cancer. Dealing with uncertainty is difficult—and often painful—for people who are struggling to make a personal decision about whether to follow suggested interventions. Epidemiologists should help the public to understand uncertainty and to cope with the challenge of making decisions in the face of equivocal and incomplete information.

An additional question is: At what point does a reported trivial increase in a risk ratio, even if it is statistically significant, become a biologically significant risk that merits public concern? This question relates to the overall issue of public perceptions of risk. These perceptions are reflected in Tables 20.1 and 20.2. For many of the risks listed, the degree of public concern and the change in behavior do not seem commensurate with the magnitude of the risk.

If the absolute risk is low, even if the relative risk in exposed individuals is significantly increased, the actual risk to exposed individuals will still be very low. It is interesting that the public often prefers to address "hot" issues (such as a reported risk from alar in apples), for which the evidence may be tenuous, while ignoring well-established risk factors such as smoking, alcohol consumption, and sun exposure, for which lifestyle changes that are dependent on individual initiative are clearly warranted by the available evidence.

TABLE 20.1 Involuntary Risks

Involuntary Risk	Risk of Death per Person per Year
Struck by automobile (United States)	1 in 20,000
Struck by automobile (United Kingdom)	1 in 16,600
Floods (United States)	1 in 455,000
Earthquake (California)	1 in 588,000
Tornadoes (Midwest)	1 in 455,000
Lightning (United Kingdom)	1 in 10 million
Falling aircraft (United States)	1 in 10 million
Falling aircraft (United Kingdom)	1 in 50 million
Release from an atomic power station	
At site boundary (United States)	1 in 10 million
At 1 km (United Kingdom)	1 in 10 million
Flooding of a dike (The Netherlands)	1 in 10 million
Bites of venomous creatures (United Kingdom)	1 in 5 million
Leukemia	1 in 12,500
Influenza	1 in 5,000
Meteorite	1 in 100 billion

From Dinman BD. The reality and acceptance of risk. *JAMA*. 1980;244:1226. Copyright 1980, American Medical Association.

Epidemiologists have a major function in communicating health risks and interpreting epidemiologic data for nonepidemiologists; if epidemiologists do not participate in this activity, it will be left to others with far less training and expertise. This is an essential part of the policy-making process. Studies of human populations often yield different findings, and epidemiologists often hesitate to draw conclusions on the basis of existing data. In academic settings, epidemiologists can criticize the design of studies and their findings, and the typical refrain is to recommend additional research to resolve an issue. However, policy makers working at the front lines do not have this luxury of delay—they must make immediate decisions (to regulate or not to regulate). Even a decision not to regulate at this time represents a policy decision. Such decisions should

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TABLE 20.2 Voluntary Risks

Voluntary Risk	Risk of Death per Person per Year
Smoking: 20 cigarettes/day	1 in 200
Drinking: 1 bottle of wine/day	1 in 13,300
Soccer, football	1 in 25,500
Automobile racing	1 in 1,000
Automobile driving (United Kingdom)	1 in 5,900
Motorcycling	1 in 50
Rock climbing	1 in 7,150
Taking oral contraceptive pills	1 in 5,000
Power boating	1 in 5,900
Canoeing	1 in 100,000
Horse racing	1 in 740
Amateur boxing	1 in 2 million
Professional boxing	1 in 14,300
Skiing	1 in 430,000
Pregnancy (United Kingdom)	1 in 4,350
Abortion: Legal <12 weeks	1 in 50,000
Abortion: Legal >14 weeks	1 in 5,900

From Dinman BD. The reality and acceptance of risk. *JAMA*. 1980;244:1226. Copyright 1980, American Medical Association.

ideally capitalize on existing epidemiologic findings. However, policy makers cannot act in a rational fashion by waiting for findings from future studies to direct their actions regarding current pressing health issues. Epidemiologists must therefore draw the best conclusions possible on the basis of currently available data, fully realizing that a better study, or even a perfect study, may appear tomorrow and may contradict today's conclusions.

Epidemiologists have several roles in the process of policy making, including generating and interpreting the data, presenting specific policy options that are consistent with the data, projecting the impact of each option, developing specific policy proposals, and evaluating the effects of policies after they have been implemented. Should an epidemiologist be both a researcher and an advocate for a specific policy? Does advocacy for a position imply a loss of objectivity and of scientific credibility? These are difficult questions, but many clear issues, such as the health hazards resulting from cigarette smoking, urgently need the participation of epidemiologists in the struggle to eliminate this source of the danger to the public's health. The question then is not only whether it is ethical for an epidemiologist to be an advocate but whether it is ethical for an epidemiologist *not* to be an advocate when the evidence of risk is so convincing. Thus the epidemiologist must serve as an educator as well as a researcher. The epidemiologist's educational efforts are directed at many target populations, including other scientists, other health professionals, legislators, policy makers, lawyers, judges, and the public. Each group must be dealt with differently, depending on its specific needs and on the objectives toward which the educational effort is directed. Epidemiologists must learn to work with the media, including radio, television, magazines, and newspapers, and, increasingly, with social media, in order to further their educational efforts. Epidemiologists should also familiarize themselves with what is known about how risks are perceived by patients, health care providers, and the general public so that they can help these groups deal with the findings of epidemiologic studies and with their implications for preventive measures, including lifestyle changes.[23]

CONCLUSION

The ethical and professional issues facing epidemiology primarily relate to epidemiologists' obligations to participants in their epidemiologic studies, as well as the overall challenge of a discipline that lies at the interface of science and public policy. The issues are complex, often subtle, and without simple direct answers. Given the pivotal position of epidemiology in the development of both clinical and public health policy and its implications for environmental regulation, individual lifestyle changes, and rapid changes in clinical practice, the findings from epidemiologic studies attract widespread attention and high public visibility. As new questions are addressed by epidemiology in the future, the ethical and professional dilemmas facing the discipline will also continue to evolve. It is critical that dialogue continues between epidemiologists and those who use the results of epidemiologic studies, including policy makers and physicians, as well as the public who will be affected by new health and prevention policies.

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ANSWERS

Chapter 1

No Review Questions

Chapter 2

1. b
2. a
3. b
4. d
5. c
6. c

Chapter 3

1. e
2. 10%
3. c
4. c
5. d
6. b
7. c
8. c
9. d
10. d

Chapter 4

1. 5/1,000
2. 30%
3. e
4. b
5. b
6. a
7. 2.5 or 250
8. d
9. c
10. d
11. 9.6/1,000
12. e
13. d
14. a
15. b

Chapter 5

1. 72.0%
2. 84.0%
3. 69.2%
4. d
5. d
6. b
7. 3.3%
8. b
9. 70.0%
10. 57.1%
11. 0.4
12. b

Chapter 6

The answers to questions 6 through 8 are based on calculating and completing the table provided (as shown later in this section).

1. 54.8%
2. c
3. c
4. b
5. c
6. 0982 or 98.2%
7. 0.006 or 0.06%
8. c
9. a
10. b

Chapter 7

1. c
2. a
3. c
4. b
5. c
6. d
7. e
8. d
9. c
10. c
11. c

Chapter 8

1. d
2. a
3. c
4. a
5. c
6. d
7. b

Chapter 9

No Review questions

Chapters 10 and 11

1. e
2. e
3. c
4. b
5. b
6. a
7. c
8. 57
9.
   9a. b
   9b. c
   9c. e
   9d. d
   9e. a
10. 0.67
11. 36

Chapter 12

1. 15.3
2. d
3. e
4. e
5. 4.5
6. 6.3
7. 1:7 (0.143)
8. e
9. e
10. 1.94
11. 1.50
12. The odds of prostate cancer are 50% higher among never aspirin users compared to ever aspirin users.
13. b

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Chapter 13

1. b
2. 27.5/1,000
3. 84.6%
4. 3.6/1,000
5. 78.3%

Chapter 14

1. c
2. a
3. e
4. b
5. d

Chapter 15

1. e
2. c
3. c
4. 12
5. 18.7
6. 9
7. 6.2
8. d
9. b

Chapter 16

1. c
2. c
3. b
4. b
5. c

Chapter 17

1. b
2. b
3. a
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INTERACTIVE SELF ASSESSMENTS TO APPEAR ON STUDENT CONSULT

CHAPTERS 2–4 REVIEW QUESTIONS (44 QUESTIONS)

1. Which of the following is a condition which may occur during the incubation period?
   - **a.** Onset of clinical illness
   - **b.** Receipt of infection
   - **c.** Signs and symptoms of disease
   - **d.** **Transmission of infection**
   - **e.** Isolation of disease carrier through quarantine

The incubation period is defined as the interval from receipt of infection to the time of onset of clinical illness. Accordingly, individuals may transmit infectious agents during the incubation period as they show no signs of disease that would enable the isolation of sick individuals by quarantine.

2. Chicken pox is a highly communicable disease. It may be transmitted by direct contact with a person infected with the varicella-zoster virus (VZV). The typical incubation time is between 10 and 20 days. A boy started school 2 weeks after showing symptoms of chicken pox including mild fever, skin rash, and fluid-filled blisters. One month after the boy returned to school, none of his classmates had been infected by VZV. The main reason was:
   - **a.** Herd immunity
   - **b.** All had been immunized prior to the school year
   - **c.** **Contact was after infectious period**
   - **d.** Subclinical infections were not yet detected
   - **e.** Disease was endemic in the class

The disease is spread by contact with an infected individual who can transmit the agent (VZV) to immunologically naive persons during the incubation period and for several days after onset of clinical illness. Since the boy started school 14 days after showing signs consistent with chicken pox, it is most likely that he was no longer infectious.

3. The ability of a single person to remain free of clinical illness following exposure to an infectious agent is known as:
   - **a.** Hygiene
   - **b.** Vaccination
   - **c.** Herd immunity
   - **d.** **Immunity**
   - **e.** Latency

Immunity is the capacity of a single individual to avoid disease susceptibility when exposed to an infectious agent. Herd immunity is a population characteristic. For certain diseases, individual immunity can be acquired by vaccination, but this is not true for all infectious diseases.

4. Which of the following is characteristic of a single-exposure, common-vehicle outbreak?
   - **a.** Long latency period before many illnesses develop
   - **b.** There is an exponential increase in secondary cases following initial exposures
   - **c.** Cases include only those who have been exposed to sick persons
   - **d.** **The epidemic curve has a normal distribution when plotted against the logarithm of time**
   - **e.** Wide range in incubation times for sick individuals

Single-exposure, common-vehicle outbreaks involve a sudden, rapid increase in cases of disease that are limited to persons who share a common exposure. Additionally, few secondary cases develop among persons exposed to primary cases. A histogram of the outbreak can plot the number of cases by time of disease onset. In single-exposure, common-vehicle outbreaks, a log transformation of the time of disease onset will often take on the characteristic shape of a normal distribution (i.e., a bell curve) with the median incubation time found at the peak of the curve.

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5. What is the diarrhea attack rate in persons who ate both ice cream and pizza?

	ATE ICE CREAM		DID NOT EAT ICE CREAM	
	Diarrhea	**Total**	**Diarrhea**	**Total**
Ate pizza	39	52	14	40
Did not eat pizza	11	15	9	30

a. 39/52
b. 21/70
c. 39/67
d. 51/67
e. None of the above

The attack rate in this example is defined as the number of persons who develop diarrhea divided by the total number of people at risk. In this example, the at-risk group is those who have eaten both ice cream and pizza. Of these 52 persons, 39 developed diarrhea.

6. What is the overall attack rate in persons who did not eat ice cream?

	ATE ICE CREAM		DID NOT EAT ICE CREAM	
	Diarrhea	**Total**	**Diarrhea**	**Total**
Ate pizza	39	52	14	40
Did not eat pizza	11	15	9	30

a. 30%
b. 33%
c. 35%
d. 44%
e. 58%

The attack rate is the number of persons with diarrhea (14 + 9) divided by the total number of persons who did not eat ice cream (40 + 30).

7. Which of the food items (or combination of items) is most likely to be the infective item(s)?

	ATE ICE CREAM		DID NOT EAT ICE CREAM	
	Diarrhea	**Total**	**Diarrhea**	**Total**
Ate pizza	39	52	14	40
Did not eat pizza	11	15	9	30

a. Pizza only
b. Ice cream only
c. Neither pizza nor ice cream
d. Both pizza and ice cream
e. Cannot be assumed from the data shown

Among persons eating ice cream, over 70% developed diarrhea regardless of their pizza consumption (39/52 and 11/15). Among both groups of persons who did not eat ice cream, each attack rate was equal to or less than 35% (14/40 and 9/30).

8. Which of the following reasons can explain why a person who did not consume the infective food item got sick?

	ATE ICE CREAM		DID NOT EAT ICE CREAM	
	Diarrhea	**Total**	**Diarrhea**	**Total**
Ate pizza	39	52	14	40
Did not eat pizza	11	15	9	30

a. They were directly exposed to persons who did eat the infective food item
b. Diarrhea is a general symptom consistent with a number of illnesses
c. There may have been an inaccurate recall of which foods were eaten
d. All of the above
e. None of the above

Without knowledge as to the specific agent in this instance, it is also likely that it can be spread by direct contact with infected persons. Since diarrhea is a general disease symptom, it is possible that several infectious agents may be present at this meal or others eaten during the same time period. Furthermore, information regarding food consumption may have been collected long after the disease episode. This may have led persons to incorrectly remember the foods that they consumed.

9. An outbreak of gastroenteritis occurred at a boarding school with a student enrollment of 846. Fifty-seven students reported symptoms including vomiting, diarrhea, nausea, and low-grade fever between 10 p.m. on September 24 and 8 p.m. on September 25. The ill students lived in dormitories that housed 723 of the students. The table below provides information on the number of students per type of residence and the number reporting illnesses consistent with the described symptoms and onset time. Calculate the attack rate among all students at the boarding school.

Residence	Number of Students	Number of Cases
Boys' dormitory (all boys)	380	40
Girls' dormitory (all girls)	343	12
Day students (live at home)	123 (46 boys, 77 girls)	5 (3 boys, 2 girls)
Total	846	57

a. 10.5%
b. 4.0%
c. 6.7%
d. 10.5%
e. 3.5%

The overall attack rate including both girls and boys is usually called the "main effect".

10. An outbreak of gastroenteritis occurred at a boarding school with a student enrollment of 846. Fifty-seven students reported symptoms including vomiting, diarrhea, nausea, and low-grade fever between 10 p.m. on September 24 and 8 p.m. on September 25. The ill students lived in dormitories that housed 723 of the students. The table below provides information on the number of students per type of residence and the number reporting illnesses consistent with the described symptoms and onset time. Calculate the attack rates for boys and girls separately.

Residence	Number of Students	Number of Cases
Boys' dormitory (all boys)	380	40
Girls' dormitory (all girls)	343	12
Day students (live at home)	123 (46 boys, 77 girls)	5 (3 boys, 2 girls)
Total	846	57

Boys: 10.5%, Girls: 3.5% The heterogeneity between boys and girls is named "moderation" or "effect modification" and suggests a higher exposure in boys.

11. An outbreak of gastroenteritis occurred at a boarding school with a student enrollment of 846. Fifty-seven students reported symptoms including vomiting, diarrhea, nausea, and low-grade fever between 10 p.m. on September 24 and 8 p.m. on September 25. The ill students lived in dormitories that housed 723 of the students. The table below provides information on the number of students per type of residence and the number reporting illnesses consistent with the described symptoms and onset time. What is the proportion of total cases occurring in boys?

Residence	Number of Students	Number of Cases
Boys' dormitory (all boys)	380	40
Girls' dormitory (all girls)	343	12
Day students (live at home)	123 (46 boys, 77 girls)	5 (3 boys, 2 girls)
Total	846	57

The proportion of total cases in boys is 57.8% Note that the denominator is total cases, not the total at risk. To examine risk, the denominator must be the total sample at risk.

12. An outbreak of gastroenteritis occurred at a boarding school with a student enrollment of 846. Fifty-seven students reported symptoms including vomiting, diarrhea, nausea, and low-grade fever between 10 p.m. on September 24 and 8 p.m. on September 25. The ill students lived in dormitories that housed 723 of the students. The table below provides information on the number of students per type of residence and the number reporting illnesses consistent with the described symptoms and onset time. What is the proportion of total cases occurring in students who live in dormitories?

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Residence	Number of Students	Number of Cases
Boys' dormitory (all boys)	380	40
Girls' dormitory (all girls)	343	12
Day students (live at home)	123 (46 boys, 77 girls)	5 (3 boys, 2 girls)
Total	846	57

Proportion of total cases in students living in dormitories is 52/57

13. A group of researchers are interested in conducting a clinical trial to determine whether a new cholesterol-lowering agent was useful in preventing coronary heart disease (CHD). They identified 12,327 potential participants for the trial. At the initial clinical examination, 309 were discovered to have CHD. The remaining subjects entered the trial and were divided equally into the treatment and placebo groups. Of those in the treatment group, 505 developed CHD after 5 years of follow-up while 477 developed CHD during the same period in the placebo group. What was the prevalence of CHD at the initial examination?

Prevalence was 309/12,327 = 2.5%

Note that this is the point prevalence; in other words, prevalence at the time of identification of the participants.

14. A group of researchers are interested in conducting a clinical trial to determine whether a new cholesterol-lowering agent was useful in preventing coronary heart disease (CHD). They identified 12,327 potential participants for the trial. At the initial clinical examination, 309 were discovered to have CHD. The remaining subjects entered the trial and were divided equally into the treatment and placebo groups. Of those in the treatment group, 505 developed CHD after 5 years of follow-up while 477 developed CHD during the same period in the placebo group. What was the incidence of CHD during the 5-year study?

The 5-year total incidence was (505 + 477) / (12,327 − 309) = 4.4%

Note that for the calculation of incidence, only new cases are included in a population that is at risk to develop a new case; thus, existing cases at baseline must be excluded.

15. Which of the following are examples of a population prevalence proportion?

a. The number of ear infections suffered by 3-year-old children in March 2006

b. The number of persons with hypertension per 100,000 population

c. The number of cases of skin cancer diagnosed in a dermatology clinic

d. b and c

e. All of the above

Prevalence is the number of affected persons in a specified population size at a given time. Only answer (b) fits this definition.

16. What would be the effect on age-specific incidence rates of uterine cancer if women with hysterectomies were excluded from the denominator of incidence calculations, assuming that most women who have had hysterectomies are older than 50 years of age?

a. The rates in all age groups would remain the same

b. Only rates in women older than 50 years of age would tend to decrease

c. Rates in women younger than 50 years would increase compared to women older than 50 years of age

d. Rates would increase in women older than 50 years of age but may decrease in younger women as they get older

e. It cannot be determined whether the rates would increase or decrease.

Women who have had hysterectomies (i.e., removal of the uterus) are no longer at risk for uterine cancer. For women older than 50 years of age, this would increase the age-specific incidence rate as the denominator of the rate would decrease, reflecting the fact that there will be fewer women at risk. Furthermore, rates may decrease among younger women who have had hysterectomies as they are no longer at risk for uterine cancer and thus may decrease the number of potential cases occurring in their age group over time.

17. A survey was conducted among 1,000 randomly sampled adult males in the United States in 2005. The results from this survey are shown below.

Age Group	Percentage of Persons with Hypertension
18–29 years	5
30–39 years	10
40–49 years	20
50–59 years	40
60–69 years	60
70 years and older	55

The researchers stated that there was a doubling of risk of hypertension in each age group younger than 60 years of age. You conclude that the researchers' interpretation:

a. Is correct
b. Is incorrect because prevalence proportions are estimated
c. Is incorrect because it was based on proportions of the population sample
d. Is incorrect because incidence rates do not describe risk
e. Is incorrect because the calculations do not include adult females

The survey reports the disease status of a population at a specific point in time. In this case, a random sample of adult males in 2005 provides an accurate estimate of the prevalence of hypertension.

18. The incidence and prevalence proportions of a chronic childhood illness for a specific community are given below.

Based on the data, which of the following interpretations best describes disease X?

INCIDENCE AND PREVALENCE PROPORTIONS OF DISEASE X IN CHILDREN AGED 1 TO 4 YEARS

Year	Incidence Rate per 1,000 per Year	Prevalence proportion per 1,000 per Year
1975	33.2	23.8
1985	38.4	24.7
1995	41.8	24.5

a. The duration of disease is becoming shorter
b. The duration of disease is becoming longer
c. The case-fatality rate of this disease is decreasing
d. Efforts to prevent new cases of this disease are becoming more successful
e. The risk of the disease has decreased over the past 20 years

The formula for the relation between prevalence and incidence is approximately [Prevalence = Incidence × duration]; thus, duration can be estimated as Prevalence/Incidence. If incidence is increasing over time, then duration of illness has to decrease in order to keep the prevalence proportion more or less constant. This may occur through better treatments to cure disease or through higher case-fatality rates. Since incidence is increasing over time, it is evident that risk is also increasing and that prevention efforts are not successful.

19. A survey conducted from January 1 through December 31, 2003, identified 580 new cases of tuberculosis in a city of 2 million persons. The incidence rate of tuberculosis in this population has historically been 1 per 4,000 persons each year. What is the incident rate of tuberculosis per 100,000 persons in 2003?

1 per 4000 is equivalent to 25/100,000. The incidence in 2003 was 580/2,000,000 = 29/100,000. Thus, the incidence rate in 2003 was 29/100,000.

20. A survey conducted from January 1 through December 31, 2003, identified 580 new cases of tuberculosis in a city of 2 million persons. The incidence rate of tuberculosis in this population has historically been 1 per 4,000 persons each year. Has the risk of tuberculosis increased or decreased during 2003?

a. Risk remained constant
b. Risk increased
c. Risk decreased
d. A temporal tendency cannot be calculated
e. Risk cannot be calculated

- **Explanation as follows:**
  - **Incidence rate is calculated as 580/2,000,000 = 0.00029 *4,000 = 1.16 cases per 4,000 persons which is higher than previously reported incidence rate of 1 per 4,000 persons.**

21. Which of the following is an advantage of active surveillance?

a. Requires less project staff
b. Is relatively inexpensive to employ
c. More accurate due to reduced reporting burden for health care providers
d. Relies on different disease definitions to account for all cases
e. Reporting systems can be developed quickly

Active surveillance entails a concerted effort to collect information about disease occurrence. It typically involves dedicated staff members who have been specifically directed to contact physicians and hospitals in order to collect reports of disease cases in a specified

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population. This activity requires a large number of staff and resources in order to accomplish its goals.

22. The population of a city on February 15, 2005, was 36,600. The city has a passive surveillance system that collects hospital and private physician reports of influenza cases every month. During the period between January 1 and April 1, 2005, 2,200 new cases of influenza occurred in the city. Of these cases, 775 persons were ill with influenza according to surveillance reports on April 1, 2005. The monthly incidence rate of active cases of influenza for the 3-month period was:

a. 4 per 1,000 population
b. 17 per 1,000 population
c. 20 per 1,000 population
d. 39 per 1,000 population
e. 130 per 1,000 population

The monthly incidence rate is calculated based on the number of new cases of a disease developing during the 3-month time period. In this example, 2,200 cases of influenza developed among an average population of 36,600 persons at risk during the surveillance period. The incidence rate equals 2,200 divided by 36,600. In order to calculate the average monthly rate, the rate should then be divided by 3. Finally, the monthly rate can be multiplied by 1,000 in order to express it per the responses listed.

23. The population of a city on February 15, 2005, was 36,600. The city has a passive surveillance system that collects hospital and private physician reports of influenza cases every month. During the period between January 1 and April 1, 2005, 2,200 new cases of influenza occurred in the city. Of these cases, 775 persons were ill with influenza according to surveillance reports on April 1, 2005. The prevalence proportion of active influenza as of April 1, 2005, was:

a. 10 per 1,000 population
b. 14 per 1,000 population
c. 17.5 per 1,000 population
d. 20 per 1,000 population
e. Cannot be calculated as there is no information on duration

The prevalence proportion as of April 1, 2005, is equal to the number of active influenza cases reported divided by the number of persons at risk in the population at that time. The best estimate of the population size is that from the February 15 count, less those who are no longer at risk as they have already recovered from influenza and have developed immunity. Therefore, prevalence equals 705 cases divided by 36,600 less 1,495 recovered cases. This number can be multiplied by 1,000 in order to estimate a prevalence proportion of 20 cases per 1,000 persons.

24. The population of a city on February 15, 2005, was 36,600. The city has a passive surveillance system that collects hospital and private physician reports of influenza cases every month. During the period between January 1 and April 1, 2005, 2,200 new cases of influenza occurred in the city. Of these cases, 775 persons were ill with influenza according to surveillance reports on April 1, 2005. What can be inferred about influenza cases occurring in the city?

a. Active surveillance would enable better prevention of influenza
b. The incidence rate would decrease if active surveillance were employed
c. The average duration of influenza is approximately 1 month
d. The actual number of influenza cases occurring in the population is less since hospitals and private physicians may be reporting the same patients
e. The prevalence proportion should be higher since it should be calculated based on all cases of influenza occurring from January 1 through March 30, 2005

Since the average monthly incidence rate is 20 per 1,000 and the prevalence proportion is also 20 per 1,000, then the duration of disease must equal 1 month.

25. A study found that adults older than age 50 had a higher prevalence of pneumonia than those who were younger than age 50. Which of the following is consistent with this finding?

a. Younger adults have a higher incidence of pneumonia
b. Older adults have a higher case-fatality rate from pneumonia
c. Younger adults with pneumonia are more likely to report being ill than older persons
d. Incidence rates do not vary by age, but older adults have pneumonia for a longer duration compared to younger adults
e. None of the above

For prevalence to be higher among older adults, either incidence or duration of pneumonia must be increased in this age group.

26. Which of the following statements are true? More than one answer may be correct.

a. Prevalence proportions are always larger than incidence rates

b. In a steady state, the prevalence of disease is equal to the attack rate

c. Diagnostic criteria rarely impact estimates of disease prevalence and incidence

d. Prevalence proportions are useful for public health planning

e. Incidence rates can be used to estimate prevalence when the mean duration of the disease is known

- **Explanation as follows:**
  - **Prevalence can be useful in identifying burden of disease, examining time trends and suggestive of associations when the prevalence is compared between two groups (prevalence ratios).**
  - **Incidence is a measure of risk and that prevalence is not, because it does not take into account the duration of the disease. However, there is an important relationship between incidence and prevalence: in a steady-state situation, in which the rates are not changing, and in-migration equals out-migration in the populations being examined, and when the prevalence is not too high, the following equation applies: Prevalence=Incidence×Duration of Disease**

27. A disease has an incidence of 10 per 1,000 persons per year, and 80% of those affected will die within 1 year. Prior to the year 2000, only 50% of cases of the disease were detected by physician diagnosis prior to death. In the year 2000, a laboratory (lab) test was developed that identified 90% of cases an average of 6 months prior to symptom onset; however, the prognosis did not improve after diagnosis. Comparing the epidemiology of the disease prior to 2000 with the epidemiology of the disease after the development of the lab test, which statement is true concerning the disease in 2000?

a. Incidence is higher and prevalence is higher than in 1999

b. Incidence is higher in 2000 but prevalence remains the same

c. Incidence is the same in 2000 but prevalence is higher than in 1999

d. Both incidence and prevalence remain the same as in 1999

e. Incidence is the same in 2000 but prevalence is lower than in 1999

With increased ability to detect cases of the disease at earlier times, both the number of incidence and prevalent cases will increase through better detection.

28. A disease has an incidence of 10 per 1,000 persons per year, and 80% of those affected will die within 1 year. Prior to the year 2000, only 50% of cases of the disease were detected by physician diagnosis prior to death. In the year 2000, a lab test was developed that identified 90% of cases an average of 6 months prior to symptom onset; however, the prognosis did not improve after diagnosis. Which statement is true concerning the duration of the disease after the development of the lab test?

a. Mean duration of a case of the disease is shorter in 2000

b. Mean duration of a case of the disease in the same in 2000

c. Mean duration of a case of the disease is longer in 2000

d. No inference about mean duration can be made since the lab test has only been available for 1 year

Though the prognosis is similar after the development of the lab test, the duration of new cases identified by the test can be increased by up to 6 months due to earlier detection.

29. A disease has an incidence of 10 per 1,000 persons per year, and 80% of those affected will die within 1 year. Prior to the year 2000, only 50% of cases of the disease were detected by physician diagnosis prior to death. In the year 2000, a lab test was developed that identified 90% of cases an average of 6 months prior to symptom onset; however, the prognosis did not improve after diagnosis. Which statement is true concerning the disease-specific mortality rate after the development of the lab test?

a. The mortality rate for the disease is decreased in 2000

b. The mortality rate for the disease is the same in 2000

c. The mortality rate for the disease is increased in 2000

d. No inference about the mortality rate can be made since the lab test has only been available for 1 year

With the implementation of the lab test, the increase in early detection of cases will increase incidence,

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duration, and prevalence; however, since the prognosis is still the same, at least 80% of patients will die during the year 2000. This should result in a similar mortality rate to the previous year given no change in transmission, prevention, or medical care of the disease.

30. In a coastal area of a country in which a tsunami struck, there were 100,000 deaths in a population of 2.4 million for the year ending December 31, 2005. What was the all-cause crude mortality rate per 1,000 persons during 2005?

Mortality rate = 41.7/1,000

The mortality rate can be easily calculated by dividing the number of deaths by the population size and multiplying times 1,000.

31. In an industrialized nation, there were 238 deaths due to lung diseases in miners ages 20 to 64 years. The expected number of deaths in this occupational group, based on age-specific death rates for lung diseases in all males ages 20 to 64 years, was 192 during 1990. What was the standardized mortality ratio (SMR) for lung diseases in miners?

SMR = 238/192 = 1.23

The SMR is also known as the indirect method of adjustment; however, it is equivalent to a direct adjustment using the study sample (the occupational group in this example) as the standard population.

32. In 2001, a state enacted a law that required the use of safety seats for all children under 7 years of age and mandatory seatbelt use for all persons. The table below lists the number of deaths due to motor vehicle accidents (MVAs) and the total population by age in 2000 (before the law) and in 2005 (4 years after the law was enacted).

What is the age-specific mortality rate due to MVAs for children ages 0 to 18 years in 2000?

	2000		2005	
Age (yrs)	**No. of MVA Deaths**	**Population**	**No. of MVA Deaths**	**Population**
Under 7	44	3,500	20	4,000
7–18	105	21,000	80	32,000
19–49	105	57,750	240	60,000
50 or more	96	96,250	300	144,000
Total	350	178,500	640	240,000

a. 1.8 per 1,000
b. 2.9 per 1,000
c. 4.0 per 1,000
d. 6.1 per 1,000
e. Cannot be calculated from information given

The rate is found by combining the MVA deaths and total population size for the two age groups under 7 years and 7 to 18 years during the year 2000. This equals (44 + 105) divided by (3,500 + 21,000). Multiplying this rate by 1,000 persons gives the answer indicated.

33. In 2001, a state enacted a law that required the use of safety seats for all children under 7 years of age and mandatory seatbelt use for all persons. The table below lists the number of deaths due to motor vehicle accidents (MVAs) and the total population by age in 2000 (before the law) and in 2005 (4 years after the law was enacted).

Using the 2000 population as the standard population, calculate the age-adjusted mortality rate due to MVAs in 2005.

	2000		2005	
Age (yrs)	**No. of MVA Deaths**	**Population**	**No. of MVA Deaths**	**Population**
Under 7	44	3,500	20	4,000
7–18	105	21,000	80	32,000
19–49	105	57,750	240	60,000
50 or more	96	96,250	300	144,000
Total	350	178,500	640	240,000

Age-adjusted mortality = 2.8/1,000

The adjustment is done by calculating the age-specific mortality for each age (e.g., 7–18 age group = 80/32,000) and multiplying this age-specific mortality times the standard population for that age (21,000) to obtain the number of deaths. This is done for all age strata.

Summing the number of strata deaths and dividing it by the total standard population yields the age-adjusted mortality rate. The advantage of using the 2000 age-specific populations as the standard population is that the 2000 unadjusted and adjusted rates are the same.

34. In 2001, a state enacted a law that required the use of safety seats for all children under 7 years of age and mandatory seatbelt use for all persons. The table below lists the number of deaths due to motor vehicle accidents (MVAs) and the total population by age in 2000 (before the law) and in 2005 (4 years after the law was enacted).

Based on the information in the table, it was reported that there was an increased risk of death due to MVAs in the state after the law was passed. These conclusions are:

	2000		2005	
Age (yrs)	**No. of MVA Deaths**	**Population**	**No. of MVA Deaths**	**Population**
Under 7	44	3,500	20	4,000
7–18	105	21,000	80	32,000
19–49	105	57,750	240	60,000
50 or more	96	96,250	300	144,000
Total	350	178,500	640	240,000

a. Correct, because there were 1.8 times as many MVA deaths in 2005 as in 2000

b. Correct, because for each group, the mortality rates were higher in 2005 than they were in 2000

c. Correct, because both the total and the age-adjusted mortality rates due to MVA are actually lower in 2005 than in 2000

d. Incorrect, because the overall mortality rate is the same in both years

The overall crude (unadjusted) mortality rate in 2005 was 2.6 per 1,000 persons. This is found by dividing 640 deaths by a population of 240,000 persons. This rate is then multiplied by 1,000. The overall adjusted mortality rate is 2.8 per 1,000 persons as calculated in question 34. Both of these rates are higher than the overall crude mortality rate of 2.0 per 1,000 persons for the year 2000.

35. For colorectal cancer diagnosed at an early stage, the disease may have 5-year survival rates of greater than 80%. Which answer best describes early stage colorectal cancer?

a. Incidence rates and mortality rates will be similar

b. Mortality rates will be much higher than incidence rates

c. Incidence rates will be higher than mortality rates

d. Incidence rates will be unrelated to mortality rates

e. None of the above

For diseases with a long duration as indicated by high 5-year survival rates for early stage colorectal cancer, the incidence will be higher than the mortality rate since more persons are being diagnosed with the disease than are dying of it.

36. The following table gives the mean annual age-specific mortality rates from measles during the first 25 years of life in successive 5-year periods. You may assume that the population is in a steady state (i.e., migrations out are equal to migrations in).

	AGE-SPECIFIC MORTALITY RATES PER 100,000 POPULATION BY AGE GROUP				
	AGE AT DEATH (YRS)				
Year of Death	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**
1910–14	2.9	3.7	2.8	2.0	0.6
1915–19	2.4	2.8	1.7	1.5	0.4
1920–24	1.7	3.3	2.2	2.4	0.3
1925–29	1.3	2.7	2.0	1.1	0.5
1930–34	0.8	1.8	1.3	0.6	0.2
1935–39	0.5	1.7	0.9	0.2	0.1

The age-specific mortality rates for the cohort born in 1915–19 are:

a. 2.4 2.8 1.7 1.5 0.4

b. 2.9 3.7 2.8 2.0 0.6

c. 2.9 2.4 1.7 1.3 0.8

d. 2.4 3.3 2.0 0.6 0.1

e. 1.7 2.8 2.2 1.1 0.2

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This is found by tracking the cohort of children born between 1915 and 1919 by each 5-year age group (the diagonal in the table). For example, this group would be 0 to 4 years of age in 1915 to 1919 with a rate of measles mortality of 2.4. In 1920 to 1924, this group of children would be 5 to 9 years of age and have a rate of measles mortality of 3.3. Continuing in a diagonal manner, the remaining three rates can be found in the table.

37. The following table gives the mean annual age-specific mortality rates from measles during the first 25 years of life in successive 5-year periods. You may assume that the population is in a steady state (i.e., migrations out are equal to migrations in).

AGE-SPECIFIC MORTALITY RATES PER 100,000 POPULATION BY AGE GROUP

	AGE AT DEATH (YRS)				
Year of Death	**0–4**	**5–9**	**10–14**	**15–19**	**20–24**
1910–14	2.9	3.7	2.8	2.0	0.6
1915–19	2.4	2.8	1.7	1.5	0.4
1920–24	1.7	3.3	2.2	2.4	0.3
1925–29	1.3	2.7	2.0	1.1	0.5
1930–34	0.8	1.8	1.3	0.6	0.2
1935–39	0.5	1.7	0.9	0.2	0.1

Based on the information above, one may conclude:

- **a.** Age-specific mortality rates for measles decreased for the period 1910–14 to 1925–29
- **b.** Age-specific mortality rates for measles increased for the period 1910–14 to 1925–29
- **c.** The case-fatality rate decreased for the period 1910–14 to 1935–39
- **d.** Children born in 1910–14 had the highest rate of death in all periods
- **e. Children ages 5 to 9 had the highest rate of death in all periods**

For each 5-year period, the highest mortality rate is reported among those 5 to 9 years of age. This is seen by comparing the rates for this age group to those of all other age groups in a row. Note that is equivalent to saying that, independently of when the children aged 5 to 9 years were born, their rates are higher than those of the other age groups.

38. Which of the following characteristics indicate that mortality rates provide a reliable estimate of disease incidence? More than one answer may be correct.

- **a.** Case-fatality rate is low
- **b. The case-fatality rate is high**
- **c. The duration of disease is short**
- **d.** The prevalence of disease is greater than 5%
- **e.** The proportionate mortality is high

- **Explanation as follows:**
  - **In a mortality rate, the denominator represents the entire population at risk of dying from the disease, including both those who have the disease and those who do not have the disease (but who are at risk of developing the disease). In case-fatality, however, the denominator is limited to those who already have the disease. Thus, case-fatality is a measure of the severity or fatality of the disease. It can also be used to measure any benefits of a new therapy; as therapy improves, case-fatality would be expected to decline. The numerator of case-fatality should ideally be restricted to deaths from that disease. However, it is not always easy to distinguish between deaths from that disease and deaths from other causes.**

39. Which of the following statements are true? More than one answer may be correct.

- **a. A mortality rate is an example of an incidence where the case-fatality is high and the disease duration is short**
- **b.** Death certificate data are generally valid regardless of the cause of death
- **c.** Type of disease is the most important predictor of mortality
- **d.** Changing diagnostic criteria does not affect estimates of prevalence and incidence
- **e.** The case-fatality rate is calculated based on the entire population at risk

A mortality rate can approximate an incidence rate under conditions of a high case-fatality rate and a short duration of disease.

40. Among those who are 25 years of age, those who have been driving less than 5 years had 13,700 motor vehicle accidents in 1 year, while those who had been driving for more than 5 years had 21,680 motor vehicle accidents during the same time period. It was concluded from these data that 25-year-olds with more driving experience have increased accidents compared to those who started driving later. This conclusion is:

- **a.** Correct based on the data
- **b. Incorrect because rates are not reported**

c. Incorrect because prevalence estimates are given when incidence rates should be reported
d. Incorrect because there are no comparison groups identified
e. Both b and d are correct

The information provided only enumerates motor vehicle accidents in two groups. In order to fully compare these counts, information is needed on the denominators, i.e., the number of persons driving in each group, so that rates can be calculated.

41. For a disease such as liver cancer, which is highly fatal and of short duration, which of the following statements is true? Choose the best answer.
a. Mortality rates will be much higher than incidence rates
b. Mortality rates will be much higher than prevalence proportions
c. Incidence rates will be much higher than mortality rates
d. Case-fatality rates will be equal to mortality rates
e. Incidence rates will be similar to mortality rates

Since the 5-year survival rate for liver cancer is 4%, most incident cases of liver cancer will result in a premature mortality. In this case, the mortality and incidence rates will be approximately equal.

42. The prevalence proportion of a disease is two times greater in women than in men, but the incidence rates are the same in men and women. Which of the following statements may explain this situation?
a. The duration of disease is shorter in women
b. Men are at greater risk for developing the disease
c. The case-fatality rate is lower for women
d. The age-adjusted mortality rate will be higher for women
e. The proportionate mortality rate for the disease is higher for men

Since men and women develop the disease at the same rate, the survival rate in women must be increased in order to increase duration and prevalence. A low case-fatality rate would contribute to an increased duration of the disease.

43. The table below describes the number of illnesses and deaths caused by plague in four communities. The case-fatality rate (CFR) associated with plague is lowest in which community?

	Total Deaths	Death from Plague	Sick from Plague
Community A	200	100	150
Community B	400	300	400
Community C	800	300	500
Community D	5,000	500	650

a. Community A
b. Community B
c. Community C
d. Community D

The case-fatality rate equals the number of deaths occurring from plague divided by all persons with the plague. In Community C, the CFR is 300 divided by 400, or 60%. This is lower than A (67%), B (75%), and D (77%).

44. The table below describes the number of illnesses and deaths caused by plague in four communities. The proportionate mortality ratio (PMR) associated with plague is lowest in which community?

	Total Deaths	Death from Plague	Sick from Plague
Community A	200	100	150
Community B	400	300	400
Community C	800	300	500
Community D	5,000	500	650

a. Community A
b. Community B
c. Community C
d. Community D

The proportionate mortality rate equals the number of deaths occurring from plague divided by all persons with the plague. In Community D, the PMR is 500 divided by 5000, or 10%. This is lower than A (50%), B (75%), and D (38%).

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CHAPTERS 5–6 REVIEW QUESTIONS (40 QUESTIONS)

1. In a community-based hypertension testing program called HT-Aware, the detection level for high blood pressure is set at 140 mmHg for systolic blood pressure. A separate testing program called HT-Warning in the same community sets the level at 130 mmHg for high systolic blood pressure. Which statements are likely to be true?
   - **a. The sensitivity of HT-Warning is greater than that of HT-Award**
   - **b.** The specificity of HT-Warning is greater than that of HT-Aware
   - **c. The number of false positives is greater with HT-Warning than with HT-Aware**
   - **d.** The number of false negatives is greater with HT-Warning than with HT-Aware
   - **e.** The sensitivity and specificity are the same for both tests
2. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. How many children are labeled "positive" by the school nurse?

There are 150 children with myopia in the school population (15% prevalence among 1,000 children). The school nurse will identify 60% of those who truly have the condition, or 90 cases (60% sensitivity multiplied by 150 myopic children). Further, the school nurse will incorrectly identify 170 false positive cases of myopia among those who do not have the condition (80% specificity multiplied by 850 non-myopic children). The sum of the cases labeled as positive by the school nurse equals 260 children (90 true myopic children plus 170 false positive children).

3. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What is the positive predictive value (PPV) of the school nurse's examination?

The PPV of the school nurse's examination is equal to the number of true positive cases divided by the total number of those that the school nurse labels as positive. In this examination, the PPV is 34.6% (90 true myopic children divided by 260 children labeled as myopic by the school nurse).

4. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. How many children will be labeled myopic following the optometrist's examination?

Since the optometrist will only test children who have been labeled as myopic by the school nurse, the testing group for this sequential examination is 260 children. The optometrist labels 105 children as myopic. Among the 90 myopic children correctly referred by the school nurse, the optometrist identifies 88 of them as myopic (98% sensitivity multiplied by 90 true cases of myopia). Further, the optometrist will incorrectly identify 17 false positive cases among the 170 children referred by the school nurse who do not have myopia. The sum of the cases labeled as positive by the optometrist equals 105 children (88 true cases plus 17 false positive cases).

5. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What is the positive predictive value (PPV) of the optometrist's examination?

The PPV of the optometrist's examination is equal to the number of true positive cases divided by the total number that the optometrist labels as positive. The optometrist will only test 260 children referred by the school nurse. Of these children, the optometrist will correctly identify 88 cases of myopia among 105 children labeled as positive for the condition. The PPV equals 83.8% (89 true myopic children divided by 105 children labeled as positive).

6. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What is the negative predictive value (NPV) of the optometrist's examination?

The NPV of the optometrist's examination is 98.7%. The NPV equals the number of true negative cases divided by all negative cases indicated by the examination. In this instance, the optometrist correctly identifies 153 children as negative for myopia; however, there are 2 false negative cases following the optometrist's examination (90 true cases referred by the school nurse less the 88 cases detected by the optometrist). The NPV equals 153 divided by 155, or 98.7%.

7. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What is the overall sensitivity of the sequential examinations?

The overall sensitivity of the sequential examinations is 58.7%; 88 true positive cases of myopia are found following the optometrist's examination among the 150 prevalent cases in the school population.

8. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What is the overall specificity of the sequential examinations?

The overall specificity of the sequential examinations is 98%; 833 children will be correctly labeled as negative for myopia among the 850 true negative cases. This is found by summing the number of true positives after each examination (680 following that of the school nurse plus 153 following the optometrist) and dividing by the true negative children in the population. This equals 833 divided by 850, or 98%.

9. A school nurse examined a population of 1,000 children in an attempt to detect nearsightedness. The prevalence of myopia in this population is known to be 15%. The sensitivity of the examination is 60% and its specificity is 80%. All children labeled as "positive" (i.e., suspected of having myopia) by the school nurse are sent for examination by an optometrist. The sensitivity of the optometrist's examination is 98% and its specificity is 90%. What would be the positive predictive value (PPV) of the examination for myopia if the optometrist tested all 1,000 children?

The PPV of the optometrist's examination would be equal to the number of true positive cases divided by all children labeled positive by the optometrist. Applying the sensitivity and specificity of the optometrist's examination to the 1,000 children would indicate that 147 true positive cases are labeled positive by the optometrist. Additionally, the optometrist would find 85 false positive cases (850 true negative cases multiplied by 90% specificity). The PPV would be 63.4% (147 true positive cases divided by 232 total positives indicated by the optometrist).

10. Which of the following improves the reliability of diabetes screening tests?
    - **a.** Having the same lab analyze all samples
    - **b.** Taking more than one sample for each subject and averaging the results
    - **c.** Insuring that the instrument is standardized before each sample is analyzed

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d. a and c only
e. All of the above

Reliability is improved by consistency of analyses, especially when multiple samples are taken for a subject and the analytic instrument is routinely standardized.

11. A prostate specific antigen (PSA) test is a quick screening test for prostate cancer. A researcher wants to evaluate it using two groups. Group A consists of 1,500 men who had biopsy-proven adenocarcinoma of the prostate while group B consists of 3,000 age- and race-matched men all of whom showed no cancer at biopsy. The results of the PSA screening test in each group is shown in the table. What is the sensitivity of the PSA screening test in the combined groups?

	Group A	Group B
Positive for PSA screening test	1,155	240
Total in group	1,500	3,000

The sensitivity equals the number of true positives detected among all true positives. Since a biopsy is the gold standard test for prostate cancer, all 1,500 men in group A are positive for prostate cancer. The PSA test indicated that 1,155 of these men had prostate cancer, a sensitivity of 77%.

12. A prostate specific antigen (PSA) test is a quick screening test for prostate cancer. A researcher wants to evaluate it using two groups. Group A consists of 1,500 men who had biopsy-proven adenocarcinoma of the prostate while group B consists of 3,000 age- and race-matched men all of whom showed no cancer at biopsy. The results of the PSA screening test in each group is shown in the table. What is the specificity of the screening test in the combined groups?

	Group A	Group B
Positive for PSA screening test	1,155	240
Total in group	1,500	3,000

The specificity equals the number of true negatives detected among all true negatives. Among the 3,000 men who did not have prostate cancer, the test correctly identified 2,760 men as negative for prostate cancer (3,000 minus 240 false positives). This gives a sensitivity of 92%.

13. A prostate specific antigen (PSA) test is a quick screening test for prostate cancer. A researcher wants to evaluate it using two groups. Group A consists of 1,500 men who had biopsy-proven adenocarcinoma of the prostate while group B consists of 3,000 age- and race-matched men all of whom showed no cancer at biopsy. The results of the PSA screening test in each group is shown in the table. What is the positive predictive value (PPV) of the screening test in the combined groups?

	Group A	Group B
Positive for PSA screening test	1,155	240
Total in group	1,500	3,000

The PPV is 83%. This value is found by dividing 1,155 true positives by the total number of all positives indicated by the PSA test (1,155 plus 24).

14. A prostate specific antigen (PSA) test is a quick screening test for prostate cancer. A researcher wants to evaluate it using two groups. Group A consists of 1,500 men who had biopsy-proven adenocarcinoma of the prostate while group B consists of 3,000 age- and race-matched men all of whom showed no cancer at biopsy. The results of the PSA screening test in each group is shown in the table. The PSA screening test is used in the same way in two equal-sized populations of men living in different areas of the United States, but the proportion of false positives among those who have a positive PSA test in the first population is lower than that among those who have a positive PSA test in the second population. What is the likely explanation for this finding?

	Group A	Group B
Positive for PSA screening test	1,155	240
Total in group	1,500	3,000

a. It is impossible to determine what caused the difference
b. The prevalence of disease is higher in the first population
c. The specificity of the test is lower in the first population
d. The specificity of the test is higher in the first population
e. The prevalence of the disease is lower in the first population

We can assume that the specificity of the test will be similar in each population. Therefore the proportion of false positives found among the true negatives should be the same in each population. However, the proportion of

false positives among all positives on the PSA screening test will be influenced by the number of true positives detected by the test. Since the sensitivity of the test will also be the same, we can assume that more true positives exist in the population of men with a lower proportion of false positive tests due to an increase in the PPV.

15. Test A has a sensitivity of 95% and a specificity of 90%. Test B has a sensitivity of 80% and a specificity of 98%. In a community of 10,000 people with 5% prevalence of the disease, Test A has always been given before Test B. What is the best reason for changing the order of the tests?

a. The net sensitivity will be increased if Test B is given first
b. The total number of false positives found by both tests is decreased if Test B is given first
c. The net specificity will be decreased if Test B is given first
d. The total number of false negatives found by both tests is decreased if Test B is given first
e. There is no good reason to change the order of the tests

A sequential testing process would only refer those with positive results to the second test. Since Test B has a higher specificity, then fewer false positives will be referred for Test A, thereby decreasing the number of false positives found. This can be shown by calculation if we assume that 500 persons have the disease among the 10,000 in the population. Test B will find only 190 false positives for referral (9,500 true negatives less the number of true negatives multiplied by 98% specificity). Performing Test A first results in 950 false positives referred for the second test (9,500 true negative less the number of true negatives multiplied by 90% specificity).

16. Two neurologists, Drs. J and K, independently examined 70 magnetic resonance images (MRIs) for evidence of brain tumors. As shown in the table below, the neurologists read each MRI as either "positive" or "negative" for brain tumors.

		Dr. J	
		Positive	**Negative**
Dr. K	Positive	26	12
	Negative	14	18

Based on the above information, the overall percent agreement between the two doctors including all observations is:

a. 37.1%
b. 62.9%
c. 65.0%
d. 68.4%
e. 84.6%

The two doctors agree on 44 of the 70 MRI readings. This includes the 26 that they both labeled as positive for brain tumors and the 18 that they both agreed were negative for brain tumors.

17. Two neurologists, Drs. J and K, independently examined 70 magnetic resonance images (MRIs) for evidence of brain tumors. As shown in the table below, the neurologists read each MRI as either "positive" or "negative" for brain tumors.

		Dr. J	
		Positive	**Negative**
Dr. K	Positive	26	12
	Negative	14	18

What is the estimate of kappa for the reliability of the two doctors' test results?

a. 10.1%
b. 24.9%
c. 50.6%
d. 57.4%
e. 68.4%

The estimate of kappa expresses the observed agreement of two testers in excess of chance alone. It is found by applying the expected agreement rates for both testers. In this case, Dr. K labeled 38 of the 70 MRIs as positive (54.3% of all MRIs) and 32 as negative (45.7% of all slides). Dr. J labeled 57.1% of the MRIs as positive (40 of 70) and 42.9% as negative. We would expect that if Dr. K had the same rate of positive and negative findings as Dr. J then they would agree by chance on 21.7 of the 38 positive MRIs that were found (38 multiplied by 0.571). Further, they would agree by chance on 13.7 of the 32 negative MRIs that were found (32 multiplied by 0.429). Therefore, we would expect the two doctors to agree by chance on 50.6% of the MRIs (21.7 positive agreements plus 13.7 negative agreements equals 35.4; then divide this by the total of 70 to get an expected overall agreement of 50.6%). Now, kappa can be calculated as the observed agreement less expected divided by 100% less the expected agreement—in this instance, (62.9% − 50.6%) / (100% − 50.6%), which is 12.3% divided by 49.4%. This results in a kappa of 24.9%.

18. This table represents the results of coronary magnetic resonance (CMR) angiography compared to x-ray angiography (the gold standard in diagnosis of coronary artery disease) in a high-risk population of patients scheduled to undergo x-ray angiography for suspected coronary artery disease.

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	Positive X-ray	Negative X-ray
Positive CMR	56	25
Negative CMR	4	18

In the general population, the prevalence of coronary artery disease is approximately 6%. Assuming that this sample of patients is representative of the general population, the sensitivity of the CMR test in the general population would be approximately:

a. Less than 75%
b. Between 75% and 85%
c. Between 85% and 90%
d. Between 90% and 95%
e. Greater than 95%

If we assume that the prevalence of disease is similar, then we can accept that 60 persons with a positive x-ray will be true cases of coronary artery disease. In this instance, the CMR test positively identifies 56 of the 60 true cases, a sensitivity of 93.3%.

19. This table represents the results of coronary magnetic resonance (CMR) angiography compared to x-ray angiography (the gold standard in diagnosis of coronary artery disease) in a high-risk population of patients scheduled to undergo x-ray angiography for suspected coronary artery disease.

	Positive X-ray	Negative X-ray
Positive CMR	56	25
Negative CMR	4	18

After reviewing the results of the test comparison, an epidemiologist decides that the specificity of the test is too low. Using the same CMR images, he raises the cutoff value for a positive test to increase the specificity. What is the likely effect on the sensitivity?

a. Sensitivity will increase
b. Sensitivity will decrease
c. There will be no effect because the two characteristics are unrelated
d. The effect cannot be predicted as it will depend on the prevalence rate
e. Sensitivity will be higher if the positive predictive value is increased

The increase in the cutoff value for a positive test will reduce the sensitivity of the test even though the specificity is increased. This will result in the misidentification of true positive cases as false negatives if their CMR values are below the cutoff value suggested by the epidemiologist.

20. In comparing the mammography readings of two technicians who evaluated the same set of 600 mammograms for presence of breast cancer from a generally representative sample of women from the population,

a. Agreement regarding negative or normal mammograms is likely to be low
b. The kappa statistic measures agreement due to chance only
c. Overall percent agreement calculated for both readers may conceal significant disagreements regarding positive tests
d. A kappa of 0.9 would be unsatisfactory
e. A kappa of 0.6 represents poor agreement

Since the sample is from the general population, it is likely that very few will have prevalent breast cancer indicating that many readings will be regarded as normal, or negative for the disease. Since a large proportion of the readings will be negative, it is likely that the two technicians will have a high value for overall percent agreement though they may differ significantly in their readings for the few women who are labeled positive for breast cancer.

21. In a country with a population of 16 million people, 175,000 deaths occurred during the year ending December 31, 2005. These included 45,000 deaths from tuberculosis (TB) in 135,000 persons who were sick with TB. Assume that the population remained constant throughout the year. What was the annual mortality rate for the country during 2005?

The annual mortality rate equals the number of deaths divided by the total population. In this example, 175,000 deaths occurred among 16 million persons. Dividing these numbers and multiplying by 100,000 gives a rate of 1,094 deaths per 100,000 persons, approximately 1% of the population.

22. In a country with a population of 16 million people, 175,000 deaths occurred during the year ending December 31, 2005. These included 45,000 deaths from tuberculosis (TB) in 135,000 persons who were sick with TB. Assume that the population remained constant throughout the year. What was the case-fatality rate (CFR) from TB during 2005?

The CFR is the number of cause-specific deaths divided by all cases of the specific disease. In this example, 45,000 TB deaths occurred in 135,000 persons with TB. This equals a CFR of 33%.

23. In a country with a population of 16 million people, 175,000 deaths occurred during the year ending December 31, 2005. These included 45,000 deaths from

tuberculosis (TB) in 135,000 persons who were sick with TB. Assume that the population remained constant throughout the year. What is the proportionate mortality ratio (PMR) for TB during 2005?

The PMR is the number of deaths due to a specific cause divided by all deaths. In this example, the PMR equals 45,000 TB deaths divided by 175,000 deaths, or approximately 26%.

24. In a country with a population of 16 million people, 175,000 deaths occurred during the year ending December 31, 2005. These included 45,000 deaths from tuberculosis (TB) in 135,000 persons who were sick with TB. Assume that the population remained constant throughout the year. Not all 135,000 cases of TB were contracted during 2005. Which of the following statements is true?

a. The case-fatality rate provides a reasonable estimate of incidence
b. The prevalence of TB for 2005 is equal to the denominator of the case-fatality rate
c. The duration of TB is brief
d. All of the above
e. None of the above

Since the duration of TB can be longer than 1 year, neither disease incidence nor prevalence can be validly estimated by mortality indicators.

25. Which of the following statements pertains to relative survival?

a. Refers to survival of first-degree relatives
b. Is equal to the case-fatality rate
c. Is generally closer to observed survival rates in younger age groups
d. Is generally closer to observed survival rates in older age groups
e. Provides an estimate of proportionate mortality

Relative survival is close to observed survival rate when there are few competing causes of death. This occurs primarily in younger age groups who are less likely to experience mortality events compared to older age groups.

26. What was the probability of surviving the second year given survival to the end of the first year?

Year of Follow-up	Number Alive at Start of Year	Number of Deaths during Year
1	1,000	50
2	950	30
3	920	10

The probability of surviving the second year given survival to the end of the year indicates that we are concerned with the survival proportion of those alive at the end of year 1. In this example, we have 950 persons alive at the beginning of year 2 (thus, the end of year 1). Of this group, 30 die by the end of the second year. This gives a survival rate of 920 divided by 950, or 97%.

27. What was the cumulative probability of surviving after only 2 years of follow-up?

Year of Follow-up	Number Alive at Start of Year	Number of Deaths during Year
1	1,000	50
2	950	30
3	920	10

The cumulative survival is the total number of those surviving by the end of the second year divided by all persons who were alive at the beginning of follow-up. In this example, there were 920 survivors among the 1,000 persons who were alive at the beginning of observation. This equals a cumulative survival of 92% Alternatively, this cumulative survival can be calculated by multiplying the survival rates for each period of interest. In this example 95% survival for year 1 multiplied by 97% survival for year 2, which equals a cumulative survival of 92%.

28. An important assumption in this type of analysis is that:

Year of Follow-up	Number Alive at Start of Year	Number of Deaths during Year
1	1,000	50
2	950	30
3	920	10

a. No change has occurred in the effectiveness of treatment during the 3-year period
b. Treatment has improved during the period of the study
c. Persons lost to follow-up are counted in the table
d. The data are age-adjusted
e. Both a and c

An important assumption of survival analysis is that separate strata, in this example, years of follow-up, have similar underlying rates of survival. If some external factor were to differentially influence survival

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during a portion of the follow-up time, then we would not be able to assume a cumulative survival that is consistent during the entire study period.

29. Complete the table. What is the probability that a person enrolled in the study will survive to the end of the third year?

(1) Interval Since Beginning Treatment	(2) Alive at Beginning of Interval	(3) Died during Interval	(4) Withdrew during Interval	(5) Effective Number Exposed to Risk of Dying during Interval: Col(2) – 1/2[Col(4)]	(6) Proportion Who Died during Interval Col (3)/Col(5)	(7) Proportion Who Did Not Die during Interval 1-Col(6)	(8) Cumulative Survival
x	l_x	d_x	w_x	l_x	q_x	p_x	P_x
1–12 months	356	80	12				
13–24 months	264	58	18				
25–36 months	188	34	8				

Note: Carry out your calculations in the table to 3 decimal places (e.g., 0.123)

The answer is 48.6%. Completing the table gives the following results for each column:
Column 5 from top to bottom: 350, 255, 184
Column 6 from top to bottom: 0.229, 0.228, 0.185
Column 8 from top to bottom: 0.771, 0.596, 0.486
The cumulative survival at the end of the follow-up period equals the probability of survival during each of the years of follow-up. In this example, multiplying 0.771 by 0.772, then multiplying this product by 0.815 equals the cumulative survival rate of 0.486.

30. Before reporting the results of this survival analysis, the investigators compared baseline characteristics of the 38 people who withdrew from the study before its end to those who had complete follow-up. This was done for which of the following reasons:

(1) Interval Since Beginning Treatment	(2) Alive at Beginning of Interval	(3) Died during Interval	(4) Withdrew during Interval	(5) Effective Number Exposed to Risk of Dying during Interval: Col(2) – 1/2[Col(4)]	(6) Proportion Who Died during Interval Col (3)/Col(5)	(7) Proportion Who Did Not Die during Interval 1-Col(6)	(8) Cumulative Survival
x	l_x	d_x	w_x	l_x	q_x	p_x	P_x
1–12 months	356	80	12				
13–24 months	264	58	18				
25–36 months	188	34	8				

a. To test whether randomization was successful
b. To check for changes in treatment
c. To check whether those remaining in the study represent the total study population
d. To check whether the survival estimate of those remaining in the study is the same as the general population
e. To check that the survival estimate for those lost to follow-up is the same as the general population

A key assumption for the use of survival analysis is that persons who are lost to follow-up have the same mortality experience as those remaining in the study (which statisticians called "uninformative censored observations"). The failure to satisfy this assumption introduces a bias in the survival estimates since the observed population has different attributes that are associated with survival compared to the population that is lost to follow-up.

31. Which of the following is a key assumption involved in the use of life-table analysis?
a. The risk of disease does not change within each interval over the period of observation
b. There are no losses to follow-up in the study population
c. The frequency of exposure is similar in treatment and comparison groups
d. The disease is common
e. The study subjects are representative of the population from which they were drawn

Life-table analysis depends upon a consistent rate of survival during all periods of the study. Changes in the probability of survival may be due to external influences that are operating at later times on only a portion of the initial population. Since those who have died earlier in the study period will not experience these external influences, the comparison between periods is rendered invalid.

32. Which of the following is a measure of disease prognosis?
a. Prevalence
b. Median survival time
c. Age-adjusted mortality rates
d. Standardized mortality ratio
e. Proportionate mortality ratio

Disease prognosis indicates the likelihood of survival once a disease has become manifest. The median survival time reflects the length of time that the 50th percentile of affected persons has. It differs from the mean survival time in that the mean survival time is an average that may be influenced by extremely low or high survival times. The median survival time consists of an ordering of all survival times with the midpoint of the distribution taken as the duration of survival.

33. In 2003, sudden acute respiratory syndrome (SARS) appeared in several countries, mainly in Asia. The disease was determined to have been caused by a virus that could be spread from person to person from the index case occurring in mainland China. This table reflects the total number of reported cases of SARS and deaths among those cases as best as can be determined.

Country	Number of Cases of SARS	Number of Deaths from SARS
Canada	249	37
China, Mainland	5,326	347
China, Hong Kong	1,755	296
China, Taiwan	687	84
Singapore	206	31
United States	75	0
Vietnam	63	5
Total	8,458	807

What is the overall case-fatality rate for the worldwide epidemic of SARS?
a. 9.5%
b. 12.4%
c. 16.0%
d. Cannot be determined as the data are not age-adjusted
e. Cannot be determined as the total number of all deaths is not known

This can be found by dividing the total number of deaths due to SARS by the total number of cases. This equals a case-fatality rate of 9.5%.

34. In 2003, sudden acute respiratory syndrome (SARS) appeared in several countries, mainly in Asia. The disease was determined to have been caused by a virus that could be spread from person to person from the index case occurring in mainland China. This table reflects the total number of reported cases of SARS and deaths among those cases as best as can be determined.

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China, Taiwan	687	84
Singapore	206	31
United States	75	0
Vietnam	63	5
Total	8,458	807

Based on the table, we can conclude that the case-fatality rate (CFR) in Vietnam:

a. Is the same as the case-fatality rate in Singapore
b. Is twice as great as the case-fatality rate in Singapore
c. Is almost one-half that of the case-fatality rate in Singapore
d. Cannot be determined because the data are not age-adjusted
e. Depends on the number of secondary cases

The CFR in Vietnam equals 5 divided by 63, or 7.9%, while that of Singapore equals 15%. This is approximately one half the rate.

35. In 2003, sudden acute respiratory syndrome (SARS) appeared in several countries, mainly in Asia. The disease was determined to have been caused by a virus that could be spread from person to person from the index case occurring in mainland China. This table reflects the total number of reported cases of SARS and deaths among those cases as best as can be determined. Following a revision in the case definition, more persons were found to have suffered from an infection with the SARS virus. The inclusion of these cases, almost all asymptomatic, did not impact the total number of SARS fatalities. What happened to the case-fatality rate (CFR) following this reclassification?

Country	Number of Cases of SARS	Number of Deaths from SARS
Canada	249	37
China, Mainland	5,326	347
China, Hong Kong	1,755	296
China, Taiwan	687	84
Singapore	206	31
United States	75	0
Vietnam	63	5
Total	8,458	807

a. It remained the same
b. It was increased
c. It was decreased
d. It cannot be determined without knowing the number of new cases
e. It cannot be determined without age-adjustment

The increase in prevalent cases with no change in mortality would decrease the CFR since the numerator, i.e., the number of deaths due to SARS, would stay the same while the denominator, i.e., the number of cases, would increased.

36. What is the probability of surviving the second year of the study given that a person survived the first year?

SURVIVAL OF PATIENTS WITH AIDS FOLLOWING DIAGNOSIS

(A) Months after Diagnosis	(B) Alive at the Start of the Interval	(C) Deaths during Interval	(D) Withdrawn during Interval	(E) Probability of Dying in the Interval	(F) Probability of Surviving the Interval	(G) Cumulative Probability of Surviving to the End of the Interval
1–12	248	96	28			
13–24		55	14			
25–36		16	2			

Note: Carry out calculations to 3 decimal places. Assume that those who withdraw are observed for one-half of the interval

The independent probability of surviving the second year for all persons who survived the first year is found by dividing the number of survivors at the end of the period by the total number present at the beginning of the period. In addition, for those who withdraw during the interval, only 50% of these persons should be counted as being present during the interval. The table should be completed with the following values.
Column (B) from top to bottom: 248, 124, 55
Column (E) from top to bottom: 0.410, 0.470, 0.296
Column (F) from top to bottom: 0.590, 0.530, 0.704
Column (G) from top to bottom: 0.590, 0.313, 0.220
Therefore, the second year survival probability among all those surviving in the study past the first year is 53%. The probability of dying during the second year equals the number of deaths during the interval (55) divided by the total number of persons alive at the start of the interval less one-half of those withdrawing from the study (117). Subtracting this value from 100% results in a survival rate of 53% for the interval.

37. For all people in the study, what is the probability of surviving to the end of the second year?

SURVIVAL OF PATIENTS WITH AIDS FOLLOWING DIAGNOSIS

(A) Months after Diagnosis	(B) Alive at the Start of the Interval	(C) Deaths during Interval	(D) Withdrawn during Interval	(E) Probability of Dying in the Interval	(F) Probability of Surviving the Interval	(G) Cumulative Probability of Surviving to the End of the Interval
1–12	248	96	28			
13–24		55	14			
25–36		16	2			

Note: Carry out calculations to 3 decimal places. Assume that those who withdraw are observed for one-half of the interval

The cumulative probability of survival through the second year equals the probability of survival for the first year multiplied by the probability for the second year. This equals 59% multiplied by 53%, or 31.3%.

38. What is the probability of surviving 3 years after diagnosis?

SURVIVAL OF PATIENTS WITH AIDS FOLLOWING DIAGNOSIS

(A) Months after Diagnosis	(B) Alive at the Start of the Interval	(C) Deaths during Interval	(D) Withdrawn during Interval	(E) Probability of Dying in the Interval	(F) Probability of Surviving the Interval	(G) Cumulative Probability of Surviving to the End of the Interval
1–12	248	96	28			
13–24		55	14			
25–36		16	2			

Note: Carry out calculations to 3 decimal places. Assume that those who withdraw are observed for one-half of the interval

The cumulative survival probability for all 3 years equals the product of the independent interval survival probabilities. In this example, 59% multiplied by 53% multiplied by 70.4% gives a cumulative survival probability of 22%.

39. What is the total number of person-years of follow-up for patients in the study assuming a median survival time of one-half of the year for all persons dying during an interval and an observation time of one-half of the year for all persons withdrawing from the study?

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SURVIVAL OF PATIENTS WITH AIDS FOLLOWING DIAGNOSIS

(A) Months after Diagnosis	(B) Alive at the Start of the Interval	(C) Deaths during Interval	(D) Withdrawn during Interval	(E) Probability of Dying in the Interval	(F) Probability of Surviving the Interval	(G) Cumulative Probability of Surviving to the End of the Interval
1–12	248	96	28			
13–24		55	14			
25–36		16	2			

Note: Carry out calculations to 3 decimal places. Assume that those who withdraw are observed for one-half of the interval

This calculation involves attributing the correct amounts of person-years to each group during an interval. For the first year of the study, 96 deaths occur. Using the median survival time, we can calculate that these persons contributed 48 person-years of observation. Additionally, 28 persons withdraw from the study. Again, allocating one-half of the year to each of these patients results in 14 person-years. Of the remaining 124 persons who survive for the full year, they contribute 124 person-years of observation. The total person-time for the first year of the study is 186 person-years. Continuing with this same approach for years 2 and 3 of the study, we arrive at a total of 321.5 person-years of observed study time.

40. Before reporting the results of this survival analysis, the investigators compared baseline characteristics of the 44 people who withdrew from the study before its end to those who had complete follow-up. This was done:

SURVIVAL OF PATIENTS WITH AIDS FOLLOWING DIAGNOSIS

(A) Months after Diagnosis	(B) Alive at the Start of the Interval	(C) Deaths during Interval	(D) Withdrawn during Interval	(E) Probability of Dying in the Interval	(F) Probability of Surviving the Interval	(G) Cumulative Probability of Surviving to the End of the Interval
1–12	248	96	28			
13–24		55	14			
25–36		16	2			

Note: Carry out calculations to 3 decimal places. Assume that those who withdraw are observed for one-half of the interval

a. To test whether randomization produced similar groups
b. To check for changes in prognosis
c. **To check whether those withdrawing from the study are similar to persons remaining in the study**
d. To check whether the outcome of those remaining in the study are the same as the underlying population
e. To check for confounders in the exposed and nonexposed group

A key assumption in life table analysis is to ensure that the experience of those lost to follow-up, or withdrawals from the study, is the same as those remaining under observation.

CHAPTERS 7–8 REVIEW QUESTIONS (15 QUESTIONS)

1. Which of the following statements best describe efficacy?
   - **a. It is an estimate of the benefit of treatment under ideal conditions**
   - **b.** It is an estimate of the benefit of treatment under routine conditions
   - **c. It is an estimate of the reduction of disease in treated groups**
   - **d.** It is an estimate of the reduction of disease in the population
   - **e.** It depends on the prevalence of disease
2. A study is conducted for a pharmaceutical agent that has shown promise for reducing heart disease among women. In order to more fully test the agent, an additional study is done restricting the participants to be randomized to those who have a history of hypertension. Which of the following advantages cannot be claimed by the researchers?
   - **a.** Power of the study is increased
   - **b.** Potential benefits in high-risk populations are increased
   - **c.** Validity of the study is increased by focus on a homogenous population
   - **d. The generalizability of the study is increased**
   - **e.** The overall cost of the study is decreased

Restricting the study to a high-risk group will only fail to increase the generalizability of the findings since the study results will apply only to a more specific group of women who share a history of hypertension.

3. A new drug treatment for cardiac thrombus claims to have a higher success rate than the current drug. A strong sign of the potential success is the lack of internal hemorrhaging starting 2 days after treatment. After agreeing to participate in a trial of the new drug, 168 patients who require treatment for cardiac thrombi are randomized. The researchers were interested in whether the new drug reduced the need for blood transfusions due to internal hemorrhage compared to the current treatment. The following table summarizes the results of the study:

	Had Blood Transfusion	Did Not Have Blood Transfusion	Death Rate in Hospital
New drug	43	41	0.250
Existing drug	26	58	0.083
Total	69	99	0.167

What is the incidence of needing a blood transfusion in the group of persons who were randomized to the new drug treatment?

- **a.** 31.0%
- **b.** 41.1%
- **c. 51.2%**
- **d.** 62.3%
- **e.** Incidence cannot be calculated with the information in this table

Incidence is the development of the outcome under investigation among those at risk. In this instance, 43 participants "developed" the need for a blood transfusion among the 84 persons in the new drug treatment group.

4. A new drug treatment for cardiac thrombus claims to have a higher success rate than the current drug. A strong sign of the potential success is the lack of internal hemorrhaging starting 2 days after treatment. After agreeing to participate in a trial of the new drug, 168 patients who require treatment for cardiac thrombi are randomized. The researchers were interested in whether the new drug reduced the need for blood transfusions due to internal hemorrhage compared to the current treatment. The following table summarizes the results of the study:

	Had Blood Transfusion	Did Not Have Blood Transfusion	Death Rate in Hospital
New drug	43	41	0.250
Existing drug	26	58	0.083
Total	69	99	0.167

What is the number of persons who died in hospital in the study?

- **a.** 7
- **b.** 17
- **c. 28**
- **d.** 35
- **e.** The number of deaths cannot be calculated as the death rate has not been age-adjusted

The death rate in the study for all participants is 0.167. Multiplying this number by 168, the total number of participants, results in 28 deaths in hospital following treatment.

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5. A new drug treatment for cardiac thrombus claims to have a higher success rate than the current drug. A strong sign of the potential success is the lack of internal hemorrhaging starting 2 days after treatment. After agreeing to participate in a trial of the new drug, 168 patients who require treatment for cardiac thrombi are randomized. The researchers were interested in whether the new drug reduced the need for blood transfusions due to internal hemorrhage compared to the current treatment. The following table summarizes the results of the study:

	Had Blood Transfusion	Did Not Have Blood Transfusion	Death Rate in Hospital
New drug	43	41	0.250
Existing drug	26	58	0.083
Total	69	99	0.167

What is the main advantage of the randomization of the 168 study participants to one of the two drug treatment groups?

- **a.** Ensures that the researchers are masked to the treatment group assignment for each participant
- **b.** Facilitates the age-adjustment of the death rate in each group
- **c. Reduces the potential for selection bias in allocation of treatment group**
- **d.** Ensures that the study groups are comparable for characteristics such as age and severity of condition prior to treatment assignment
- **e.** Ensures that noncompliance will not affect the results

Though the study is being conducted in a group of persons with a similar diagnosis, there should be differences in age, gender, race, and severity of conditions in the 168 participants. In order to ensure that those with a healthier profile are not preferentially selected for one of the treatment groups, randomization is used.

6. A new drug treatment for cardiac thrombus claims to have a higher success rate than the current drug. A strong sign of the potential success is the lack of internal hemorrhaging starting 2 days after treatment. After agreeing to participate in a trial of the new drug, 168 patients who require treatment for cardiac thrombi are randomized. The researchers were interested in whether the new drug reduced the need for blood transfusions due to internal hemorrhage compared to the current treatment. The following table summarizes the results of the study:

	Had Blood Transfusion	Did Not Have Blood Transfusion	Death Rate in Hospital
New drug	43	41	0.250
Existing drug	26	58	0.083
Total	69	99	0.167

The researchers interpret the findings to conclude that the new drug treatment is more likely to result in a blood transfusion and subsequent death. This statement is:

- **a.** Incorrect as the data do not indicate the death rate among only those receiving a blood transfusion
- **b.** Incorrect as the number of expected deaths is not known
- **c.** Incorrect as the cause-specific death rate for internal hemorrhaging is not reported
- **d.** Incorrect as the duration of time from blood transfusion to death is not reported
- **e. Correct**

Though the death rate among those receiving a transfusion cannot be directly compared with this table, the high rate of transfusion and subsequent death in the new drug treatment group strongly implies that the new drug treatment is more likely to result in these outcomes.

7. A randomized, double-blind clinical trial of a varicella vaccine observed an estimated incidence of 25% chickenpox episodes in persons receiving the vaccine, compared to 80% among persons receiving a placebo. The estimated efficacy of the vaccine is:
   - **a.** 55.0%
   - **b.** 65.0%
   - **c. 68.8%**

d. 71.4%
e. 80.0%

The efficacy is calculated by subtracting the rate in those vaccinated from the placebo rate and dividing by the placebo rate. In this example, 80% minus 25% equals 55%. Dividing by 80% results in an efficacy of 68.8%.

8. A multicenter double-blind randomized study was carried out to compare the effect of drug X with that of a placebo in patients surviving acute myocardial infarction (AMI). Treatment with the drug started 7 days after infarction in 1,884 patients, 52% of all persons who were evaluated for entry into the study. Of these 1,884 patients, 945 participants were randomized to treatment with drug X, while 939 were assigned to the placebo group. Patients were then followed for 12 months for reinfarction. There were 152 deaths in the placebo group and 98 in the group receiving drug X.

After entry into the study, patients were first classified into three groups: those who had a previous AMI, those with a first AMI who were at high risk for other cardiovascular diseases such as congestive heart failure, and those with a first AMI who were at low risk for other cardiovascular diseases. Which term best describes the study design?

a. Cohort study
b. Randomized clinical trial with crossover design
c. Randomized clinical trial with factorial design
d. Randomized clinical trial with stratified randomization
e. Case study design

The study design is a multicenter randomized clinical trial with a stratified design. The participants are classified into one of three strata, then randomized to either drug X or placebo groups. They are then followed for 1 year after entry into the study.

9. A multicenter double-blind randomized study was carried out to compare the effect of drug X with that of a placebo in patients surviving acute myocardial infarction (AMI). Treatment with the drug started 7 days after infarction in 1,884 patients, 52% of all persons who were evaluated for entry into the study. Of these 1,884 patients, 945 participants were randomized to treatment with drug X, while 939 were assigned to the placebo group. Patients were then followed for 12 months for reinfarction. There were 152 deaths in the placebo group and 98 in the group receiving drug X.

After assignment to treatment group, 77% of those in the placebo group were men, while 80% of those in the drug X group were men. Which statement is most likely to be true?

a. Randomization failed because the percentage of men is different in each group
b. Randomization failed because the researchers should have made sure that each group had an equal percentage of men
c. Randomization failed since men are more likely to have a recurrent AMI in the drug X group
d. Randomization was successful because there are more men in the treatment group
e. Randomization was successful since the investigators did not alter the selection of participants in either group in order to ensure equal percentages of men

Randomization is the process of assigning participants to a study group with nonpredictable assignment. Randomization does not guarantee equally comparable groups; however, it ensures that the researchers do not influence the selection of individual participants into a treatment group. Over large samples, characteristics will tend to be approximately equal, but this is not guaranteed since random chance can influence assignments.

10. A multicenter double-blind randomized study was carried out to compare the effect of drug X with that of a placebo in patients surviving acute myocardial infarction (AMI). Treatment with the drug started 7 days after infarction in 1,884 patients, 52% of all persons who were evaluated for entry into the study. Of these 1,884 patients, 945 participants were randomized to treatment with drug X while 939 were assigned to the placebo group. Patients were then followed for 12 months for reinfarction. There were 152 deaths in the placebo group and 98 in the group receiving drug X.

A preliminary analysis was conducted after 6 months and found that 87% of participants in the placebo group and 85% of those in the drug X group had taken

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more than 90% of their prescribed dosages. Which statement best describes this finding?

a. Randomization failed to ensure an equal likelihood of compliance with treatment
b. The characteristics of patients who failed to comply with the treatment dosages should be assessed as they may differ from those who complied
c. The study will find a decreased effect of AMI prevention in the drug X group since fewer participants complied with the prescribed treatment
d. The study will find an increased effect of AMI prevention in the placebo group since more participants complied with the prescribed treatment
e. The researchers should consider a crossover design in order to calibrate the compliance rates between each group.

The compliance rates are high and are approximately equal between the two groups so we can expect the estimated effects of treatment to be reasonably valid. An analysis should be conducted of characteristics of noncompliers as they may differ in terms of important predictors of recurrent AMI from those who take the prescribed dosages.

11. A multicenter double-blind randomized study was carried out to compare the effect of drug X with that of a placebo in patients surviving acute myocardial infarction (AMI). Treatment with the drug started 7 days after infarction in 1,884 patients, 52% of all persons who were evaluated for entry into the study. Of these 1,884 patients, 945 participants were randomized to treatment with drug X while 939 were assigned to the placebo group. Patients were then followed for 12 months for reinfarction. There were 152 deaths in the placebo group and 98 in the group receiving drug X.

Which of the following statements best describes the reason for conducting the study as a double-blind trial?

a. The placebo group will not have any reported side effects
b. The researchers might assign participants with more serious AMIs to the treatment group
c. Since the outcome studied is death, blinding the participants is unnecessary for this trial
d. Double blinding ensures that potential biases regarding selection, follow-up, and analysis can be reduced
e. Double blinding is no longer necessary after randomization is complete since the researchers cannot change the treatment group assignments

Both participants and researchers can have preconceived biases regarding the potential effect of a studied treatment. By masking the assignment of subjects from themselves and the researchers, the effect that these biases may have on the comparative analyses can be reduced.

12. A multicenter double-blind randomized study was carried out to compare the effect of drug X with that of a placebo in patients surviving acute myocardial infarction (AMI). Treatment with the drug started 7 days after infarction in 1,884 patients, 52% of all persons who were evaluated for entry into the study. Of these 1,884 patients, 945 participants were randomized to treatment with drug X while 939 were assigned to the placebo group. Patients were then followed for 12 months for reinfarction. There were 152 deaths in the placebo group and 98 in the group receiving drug X.

The researchers conclude that treatment with drug X reduces mortality in patients who have had an AMI. The researchers are:

a. Correct because there are a fewer number of deaths in the drug X group
b. Correct because the rate of death is decreased in the drug X group
c. Incorrect because noncompliance may have reduced the number of observed deaths in the drug X group compared to the placebo group
d. Incorrect because randomization was not successful
e. Incorrect as the results are not generalizable to all patients with AMI since the researchers excluded 48% of the persons evaluated for the study

The rate of death in the drug X group was 10.4%, while it was 16.2% in the placebo group. Although a statistical test such as a chi-square test should be done, the large difference in these rates between two approximately equivalent groups indicates that drug X contributed to increased survivability compared to those receiving the placebo.

13. The following data come from a study of approaches to smoking cessation. Smokers who want to quit were randomized to one of four groups: control group C who received no intervention assistance, quitting guide group Q who received brochures about how to quit smoking, quitting

guide and support group QS who received quitting brochures as well as social support brochures listing benefits of smoking cessation, and telephone support group T who received the brochures and a monthly phone call from a counselor. Participants received mailed surveys at 8, 16, and 24 months after randomization. The results after 2 years are in the table below. What is the overall quit rate after 2 years of follow-up?

	C	Q	QS	T
Quit smoking	84	71	67	109
Still smoking	381	396	404	365
Failed to return survey after 2 years	35	33	29	26

The overall quit rate after 2 years is 17.6%. This is estimated by summing the total number of those who quit smoking (331) and dividing by all participants who returned the survey after 2 years (1877).

14. The following data come from a study of approaches to smoking cessation. Smokers who want to quit were randomized to one of four groups: control group C who received no intervention assistance, quitting guide group Q who received brochures about how to quit smoking, quitting guide and support group QS who received quitting brochures as well as social support brochures listing benefits of smoking cessation, and telephone support group T who received the brochures and a monthly phone call from a counselor. Participants received mailed surveys at 8, 16, and 24 months after randomization. The results after 2 years are in the table below. Which group had the least success in terms of quitting smoking?

	C	Q	QS	T
Quit smoking	84	71	67	109
Still smoking	381	396	404	365
Failed to return survey after 2 years	35	33	29	26

a. Group C
b. Group Q
c. Group QS
d. Group T
e. It cannot be determined since each group had participants with missing outcomes

Each group has approximately equal numbers of participants with missing information. Therefore, the rates for quitting by group are 18.1% for group C, 15.2% for group Q, 14.2% for group QS, and 23% for group T. Group QS had the lowest rate of quitting among the four groups.

15. The following data come from a study of approaches to smoking cessation. Smokers who want to quit were randomized to one of four groups: control group C who received no intervention assistance, quitting guide group Q who received brochures about how to quit smoking, quitting guide and support group QS who received quitting brochures as well as social support brochures listing benefits of smoking cessation, and telephone support group T who received the brochures and a monthly phone call from a counselor. Participants received mailed surveys at 8, 16, and 24 months after randomization. The results after 2 years are in the table below. What is the main purpose of randomization in this study?

	C	Q	QS	T
Quit smoking	84	71	67	109
Still smoking	381	396	404	365
Failed to return survey after 2 years	35	33	29	26

a. To avoid assigning more persons who have tried and failed to quit in the past to the control group
b. To blind the researchers to the treatment group assignments
c. To ensure that rates of smoking cessation will be the same among groups
d. To minimize differences in the dropout rate between the groups
e. To prevent subjects in the control group from reading materials that would help them to quit smoking

The goal of randomization is to reduce selection bias in the assignment of study groups. Obviously, a participant's previous history with smoking cessation is an important predictor of his future success. In order to avoid assigning more persons who had tried and failed in the past to one specific group, randomization of all participants is the best approach.

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CHAPTERS 9–15 REVIEW QUESTIONS (69 QUESTIONS)

1. A study is planned to investigate the relationship of factors associated with maternal hypertension and the risk of congenital birth defects in children born to these women. Which of the following would be a reason for using a cohort study design?
   - **a. The need to obtain data on the incidence of early fetal losses due to congenital birth defects**
   - **b.** The low rate of congenital birth defects
   - **c.** The development of pregnancy-related hypertension in asymptomatic women
   - **d.** The consistency of recall of risk factors among women having children with and without congenital birth defects
   - **e.** Testing hypotheses about several different risk factors for congenital birth defects such as maternal age, diabetes, and previous miscarriage history

The cohort design is best for observing the incidence of a disease in persons who do not have the outcome at baseline. In this study, the researchers will start with women planning on becoming pregnant and stratify them by presence of hypertension. Since all women will be followed over time, the occurrence of fetal loss can be tracked by the investigators during the study.

2. A researcher is interested in the etiology of myocardial infarction (MI) among men between 18 and 40 years of age. Their hypothesis concerns the influence of diets high in fat and subsequent development of MI. What is the best study approach to address this hypothesis?
   - **a.** Case-control study with cases of MI identified post-event and controls sampled from healthy men in the population, then have both groups complete dietary surveys
   - **b.** Case-report study describing the dietary habits in 100 men having an MI
   - **c.** Ecologic study with the rates of MI compared between cities with higher than average dietary fat intakes and cities with lower than average dietary fat intakes
   - **d.** Non-concurrent cohort study with medical records used to collect information on diet among men with and without an MI
   - **e. Concurrent cohort study identifying a population of men in this age group, administering a dietary survey and classifying men by high- and low-fat diet, then following both groups**

The choice of a concurrent cohort study allows the researcher to select the population of interest (men aged 18 to 40 years), classify the exposure after an initial assessment, and then follow all men in the study for incident outcomes. This approach is best described as a cohort study.

3. Which of the following is an advantage to the conduct of a cohort study?
   - **a.** The study population is the same with regard to the risk factors for disease
   - **b.** The disease under study occurs rarely in the population
   - **c.** The incidence of the disease is high in the non-exposed group
   - **d. The incidence of the disease is high in the exposed group**
   - **e.** The study population includes a high number of undiagnosed, asymptomatic individuals with the disease

A cohort study entails classification of the study population by exposure to the risk factor of interest. The subsequent incidence of disease occurs during the follow-up time of observation of the study population. A high incidence of disease in the exposed group increases the statistical power of the study.

4. A cohort study is planned to investigate the potential adverse health effects of daily alcohol consumption. In assessing the risk of liver cancer related to alcoholism, which of the following is not an important methodologic consideration?
   - **a.** The need to study a large number of persons for a rare disease outcome
   - **b. The difficulty of finding enough persons with liver cancer at the beginning of the study in whom alcohol consumption could be determined**
   - **c.** The possible bias associated with persons describing alcohol usage
   - **d.** The likelihood that doctors would monitor alcoholics more closely for liver cancers

e. The possibility that persons would change their alcohol consumption practices during the study period

A cohort study must take into account the fact that a rare disease occurrence may not yield sufficient number of cases over follow-up, thus requiring a large sample size and a long follow-up period. (To study rare diseases, the case-control study design is preferred.)

5. Which of the following is not an advantage of a non-concurrent cohort study?

a. Allows for the study of many disease outcomes resulting from an exposure

b. Incidence rates can be calculated

c. Studying variables that are not part of the database

d. Potential recall bias can be minimized

e. Requires less follow-up time than a concurrent cohort study

Non-concurrent cohort studies depend on the ability of researchers to identify eligible cohort members, describe their past exposure using historical records, and to follow the cohort until the disease develops. Relying on past records to select persons for entry into the cohort study could be compromised by biases regarding the investigator's theorized association of the exposure with the disease.

6. In a study of the adverse effects of x-rays among children, a non-concurrent cohort study was done using records from several large children's hospitals for the period of 1980 to 1985. Ten thousand children were selected as a representative population of ill children seen at the hospitals during that time. Subjects were classified according to whether or not they received an x-ray during their stay in the hospital and were followed from their hospital stay through 2005 for the development of cancer. During the follow-up period, 49 incident cancers occurred in 3,263 children who had received an x-ray, and 47 incident cancers occurred in the 6,737 children who had not received an x-ray during their hospitalization. In this retrospective study, which of the following groups are eligible for selection into the study?

a. Children receiving x-rays in 1990

b. Children receiving x-rays in 1975

c. Children receiving x-rays for broken bones in 1980–85

d. Children in the hospital for cancer treatment in 1985

e. Children who were treated in private clinics and hospitals in 1981

Children who received an x-ray during the defined study period and did not have a cancer diagnosis during that time can be included in the study.

7. In a study of the adverse effects of x-rays among children, a non-concurrent cohort study was done using records from several large children's hospitals for the period of 1980 to 1985. Ten thousand children were selected as a representative population of ill children seen at the hospitals during that time. Subjects were classified according to whether or not they received an x-ray during their stay in the hospital and were followed from their hospital stay through 2005 for the development of cancer. During the follow-up period, 49 incident cancers occurred in 3,263 children who had received an x-ray, and 47 incident cancers occurred in the 6,737 children who had not received an x-ray during their hospitalization. What are the rates of cancer incidence in each exposure group?

The rate of cancer incidence in the x-ray exposed group is 15 per 1,000 (49 divided by 3,263 multiplied by 1,000) and 7 per 1,000 in the nonexposed group (47 divided by 6,737 multiplied by 1,000).

8. In a study of the adverse effects of x-rays among children, a non-concurrent cohort study was done using records from several large children's hospitals for the period of 1980 to 1985. Ten thousand children were selected as a representative population of ill children seen at the hospitals during that time. Subjects were classified according to whether or not they received an x-ray during their stay in the hospital and were followed from their hospital stay through 2005 for the development of cancer. During the follow-up period, 49 incident cancers occurred in 3,263 children who had received an x-ray, and 47 incident cancers occurred in the 6,737 children who had not received an x-ray during their hospitalization. What is the attributable risk of cancer in the exposed group due to x-ray in this study population? What is the interpretation of this estimate?

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The attributable risk equals the incidence rate in the exposed group minus the incidence rate in the nonexposed group. In this instance, the attributable risk is 8 per 1,000. This estimate is interpreted to mean that 8 of the 15 incident cases of cancer occurring in 1,000 children exposed to x-rays are due to the exposure itself.

9. In a study of the adverse effects of x-rays among children, a non-concurrent cohort study was done using records from several large children's hospitals for the period of 1980 to 1985. Ten thousand children were selected as a representative population of ill children seen at the hospitals during that time. Subjects were classified according to whether or not they received an x-ray during their stay in the hospital and were followed from their hospital stay through 2005 for the development of cancer. During the follow-up period, 49 incident cancers occurred in 3,263 children who had received an x-ray, and 47 incident cancers occurred in the 6,737 children who had not received an x-ray during their hospitalization. What is the risk ratio for the association of exposure with the development of cancer in this study? What is the interpretation of this estimated ratio?

The risk ratio is found by dividing the rate of cancers for each group (exposed and not exposed). In this instance, 15 per 1,000 (0.015) divided by 7 per 1,000 (0.007) equals a risk ratio of 2.1. This indicates that the risk of cancer is twice as high in children who received x-rays during their stay in the hospital.

10. In a study of the adverse effects of x-rays among children, a non-concurrent cohort study was done using records from several large children's hospitals for the period of 1980 to 1985. Ten thousand children were selected as a representative population of ill children seen at the hospitals during that time. Subjects were classified according to whether or not they received an x-ray during their stay in the hospital and were followed from their hospital stay through 2005 for the development of cancer. During the follow-up period, 49 incident cancers occurred in 3,263 children who had received an x-ray, and 47 incident cancers occurred in the 6,737 children who had not received an x-ray during their hospitalization. Which of the following issues should the investigators consider when interpreting whether a causal association exists between cancer incidence and childhood x-ray?
    - **a.** Some study subjects were treated for cancer starting in 1980
    - **b.** Some study subjects had parents who were diagnosed with cancer
    - **c.** Some children received x-rays at other hospitals not included in this study
    - **d.** The children were different ages when they were admitted to the hospital
    - **e. All of the above**

Each of these issues may be related to the exposure and cancer association that the investigators are reporting, and thus they must be considered. First, subjects treated for cancers in their initial hospitalization should have been excluded from the study selection. Second, genetic predisposition to cancer is an important factor pertaining to the risk of some cancers. Third, misclassified exposure may influence the relationship, especially if children received x-rays at other hospitals but did not have this fact noted in their medical records at the study hospital. Finally, age of the children is an important factor related to x-ray dosage, development, and subsequent cancer incidence. All of these issues may lead to important differences between the two defined exposure groups.

11. Which of the following may be a factor that would result from the inability to use randomization in a cohort study?
    - **a. The possibility that a factor associated with both the exposure and the disease (confounder) is not taken into account, that is, it is not adjusted for**
    - **b.** The possibility that a higher proportion of exposed persons may be included in the study
    - **c.** The possibility that a higher proportion of nonexposed persons may be included in the study
    - **d.** The study will take longer to conduct if randomization is not used
    - **e.** The possibility that several different types of diseases will develop in the study population

Randomization removes potential bias and confounding. Without this step, exposed and nonexposed groups in a cohort study may have differential distributions of confounding variables.

12. A group of 6,750 people who were free of disease X were enrolled in a cohort study in 1985 and followed with annual exams and interviews through 1995. Exposure to factor A was determined at study

enrollment and the participants were followed until 1995 to observe new cases of disease X. Data from the study at the end of follow-up are shown in the following table. What is the incidence rate of disease X among persons exposed to factor A?

Exposure to Factor A	People with Disease X	People without Disease X
Not Exposed	30	3,720
Exposed	120	2,880

a. 0.04
b. 0.19
c. 0.25
d. 4.00
e. 5.17

The incidence rate for disease X among exposed persons is found by dividing 120 (the number of people with disease X) by the total number of exposed persons (120 plus 2880). If multiplied by 100 then the incidence rate would equal 4 per 100 persons; however, this metric is not explicitly requested.

13. A group of 6,750 people who were free of disease X were enrolled in a cohort study in 1985 and followed with annual exams and interviews through 1995. Exposure to factor A was determined at study enrollment, and the participants were followed until 1995 to observe new cases of disease X. Data from the study at the end of follow-up are shown in the following table. What is the relative risk for the effect of exposure to factor A on disease X?

Exposure to Factor A	People with Disease X	People without Disease X
Not Exposed	30	3,720
Exposed	120	2,880

a. 0.20
b. 1.29
c. 4.00
d. 5.00
e. 5.17

The relative risk equals the incidence rate in the exposed divided by the incidence rate in the not exposed. In this example, the incidence rate in the exposed group is 0.04 divided by the incidence rate in the not exposed (0.008). The ratio is equal to 5.0 in this example. This indicates that the incidence rate of disease X is 5 times higher in those exposed to factor A.

14. In 2002, investigators started a study of the association of cholesterol levels and stroke in a group of 2,000 healthy persons who had participated in a cholesterol screening program in 1992. The investigators determined exposure categories using cholesterol levels in all persons who were measured at the time of the screening program. A cutoff value of 200 mg/dL was used to define "high" cholesterol, while those with levels below 200 were identified as having "low" cholesterol. Using this definition, 1,000 persons had "high" cholesterol levels, while the remaining 1,000 persons had "low" cholesterol. The investigators determined that 150 cases of stroke occurred by the end of 2004, with 113 cases occurring in the high cholesterol group. What is the study design that the investigators used?

a. Case-control study
b. Non-concurrent cohort study
c. Concurrent cohort study
d. Cross-sectional study
e. Randomized clinical trial

In this study, a study population is determined to include persons who were disease-free at baseline. Using historical records, exposure status was determined for the study population. Subsequent observation enabled the researchers to ascertain incident cases of stroke among those included.

15. In 2002, investigators started a study of the association of cholesterol levels and stroke in a group of 2,000 healthy persons who had participated in a cholesterol screening program in 1992. The investigators determined exposure categories using cholesterol levels in all persons who were measured at the time of the screening program. A cutoff value of 200 mg/dL was used to define "high" cholesterol, while those with levels below 200 were identified as having "low" cholesterol. Using this definition, 1,000 persons had "high" cholesterol levels, while the remaining 1,000 persons had "low" cholesterol. The investigators determined that 150 cases of stroke occurred by the end of 2004, with 113 cases occurring in the high cholesterol group. What type of risk measure should the investigators calculate?

a. Odds ratio
b. Prevalence rate
c. Multiplicative interaction

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d. Positive predictive value
e. Relative risk

The relative risk estimates the ratio of disease incidence in the exposed group relative to that of the nonexposed group. All other things being equal, this ratio can be interpreted to describe the relative increase (or decrease) in the incidence of disease following exposure.

16. In 2002, investigators started a study of the association of cholesterol levels and stroke in a group of 2,000 healthy persons who had participated in a cholesterol screening program in 1992. The investigators determined exposure categories using cholesterol levels in all persons who were measured at the time of the screening program. A cutoff value of 200 mg/dL was used to define "high" cholesterol while those with levels below 200 were identified as having "low" cholesterol. Using this definition, 1,000 persons had "high" cholesterol levels, while the remaining 1,000 persons had "low" cholesterol. The investigators determined that 150 cases of stroke occurred by the end of 2004, with 113 cases occurring in the high cholesterol group. Using the reported study data, what is the estimate of the risk measure that was chosen?

a. 3.1
b. 3.3
c. 67%
d. 1.0
e. 0.3

The relative risk of exposure equals 3.1 in this study. This is calculated by dividing the incidence rate for stroke among those with high cholesterol (113 divided by 1,000, or 0.113) by the incidence rate for stroke among those with low cholesterol (37 divided by 1,000, or 0.037). The ratio of these incidence rates is 3.1 and can be interpreted to indicate that stroke is 3 times more likely to occur among those with high cholesterol.

17. In 2002, investigators started a study of the association of cholesterol levels and stroke in a group of 2,000 healthy persons who had participated in a cholesterol screening program in 1992. The investigators determined exposure categories using cholesterol levels in all persons who were measured at the time of the screening program. A cutoff value of 200 mg/dL was used to define "high" cholesterol, while those with levels below 200 were identified as having "low" cholesterol. Using this definition, 1,000 persons had "high" cholesterol levels while the remaining 1,000 persons had "low" cholesterol. The investigators determined that 150 cases of stroke occurred by the end of 2004, with 113 cases occurring in the high cholesterol group. What is a necessary assumption for the study's findings to be true?

a. There is no recall bias among the study participants
b. The cholesterol level measured in 1992 is a valid determinant of exposure status during the entire study period
c. The high and low cholesterol groups are randomly assigned
d. The age distribution of the cases and controls is equivalent
e. The cholesterol measure is modified by cigarette smoking practice

Using a retrospective design to determine past exposure levels means that the exposure levels determined in 1992 must be valid for the entire follow-up period. If many of those labeled as high cholesterol had lowered their cholesterol levels during the next 12 years, then the exposure classification would be incorrect and the results of the study would not be valid.

18. The following data are from a prospective study that examined the relationship between smoking and incidence of both myocardial infarction (heart attack) and breast cancer among women. What is the proportion attributable risk of breast cancer among smokers?

	DISEASE INCIDENCE PER 1000 PERSONS PER YEAR	
Disease	**Smokers**	**Nonsmokers**
Myocardial infarction	100	80
Breast cancer	40	16

a. 20%
b. 40%
c. 50%
d. 60%
e. 80%

The proportion attributable risk (PAR) equals the incidence in the exposed less the incidence in the nonexposed divided by the incidence in the exposed. The percentage calculated expresses the proportion of the disease under investigation that can be attributed to exposure. In this study, the incidence of breast cancer in smokers is 40 per 1,000 (0.04) while the incidence in

the nonexposed is 16 per 1,000 (0.016). Subtracting the latter from the former, the difference in the incidence rate is 0.024. Dividing this difference by the incidence in smokers results in a PAR of 60%.

19. The following data are from a prospective study that examined the relationship between smoking and incidence of both myocardial infarction (heart attack) and breast cancer among women. What is the relative risk of myocardial infarction for smokers?

	DISEASE INCIDENCE PER 1000 PERSONS PER YEAR	
Disease	**Smokers**	**Nonsmokers**
Myocardial infarction	100	80
Breast cancer	40	16

a. 0.5
b. 1.0
c. 1.3
d. 2.0
e. Cannot be calculated because the nondiseased numbers are not given

The relative risk for myocardial infarction equals the incidence rate in smokers (0.1) divided by the incidence rate in nonsmokers (0.08). The ratio of these incidence rates equals 1.3. This can be interpreted to indicate that the risk of myocardial infarction is 1.3 times greater in smokers compared to nonsmokers.

20. The following data are from a prospective study that examined the relationship between smoking and incidence of both myocardial infarction (heart attack) and breast cancer among women. If the proportion of smokers in this population is 30%, what is the population proportion attributable risk of breast cancer due to smoking?

	DISEASE INCIDENCE PER 1000 PERSONS PER YEAR	
Disease	**Smokers**	**Nonsmokers**
Myocardial infarction	100	80
Breast cancer	40	16

a. 28%
b. 31%
c. 43%
d. 56%
e. 80%

The population proportion attributable risk (PPAR) equals the incidence in the total population less the incidence in the nonexposed divided by the incidence in the total population. In order to calculate the incidence in the total population, a weighted average of the two incidence rates must be calculated. The weighting factor is the prevalence of exposure in the total population. In this example, the incidence rate for the total population equals the incidence rate in smokers multiplied by the percentage of smokers plus the incidence rate in nonsmokers multiplied by the percentage of nonsmokers in the total population. In this data, the total population incidence is (0.04 × 0.3) + (0.016 × 0.7). This gives a total population incidence of 0.023, or 23 per 1,000 persons. Obviously, this incidence rate is much closer to the incidence rate in nonsmokers as the majority of the population does not smoke. Using the total population incidence in the PPAR calculation then gives an estimate of 31%. This is found by subtracting 0.016 from 0.023 and dividing this result by 0.023.

21. A researcher is interested in the etiology of cervical cancer among women between 18 and 35 years of age. Their hypothesis concerns the influence of sexually transmitted diseases such as human papilloma virus (HPV) and subsequent development of cancer. What is the best study approach to address this hypothesis?

a. Case-control study of women 18 to 35 years of age identified with cervical cancer in the hospital (cases) compared to women admitted for other diseases (controls)
b. Descriptive study of 100 cases of cervical cancer
c. Concurrent cohort study of women enrolled at 18 years of age and followed to 35 years of age
d. Non-concurrent cohort study of women identified with cervical cancer
e. Clinical trial randomizing women to HPV vaccine or placebo

The case-control design provides the most efficient comparative study approach. Women of eligible ages can be recruited on the basis of cervical cancer diagnosis, and the hospital-based non–cervical cancer population provides a valid control group with the ability to match on age and other factors.

22. Suppose that 350 cervical cancer cases were identified and a random sample of women of the same age range who were admitted to the hospital included

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500 eligible controls. After independent blood tests of all cases and controls, 90% of cases were positive for HPV antibodies while 63% of controls were positive for antibodies to the virus. What is the appropriate ratio measure of association and its value?

a. The ratio of HPV-exposed percentages is equal to 1.4
b. The ratio of nonexposed percentages is equal to 4.1
c. The number of exposed cases divided by the number of exposed controls is equal to 1.0
d. The number of nonexposed cases divided by the number of nonexposed controls is equal to 0.2
e. The ratio of the odds of exposure among cases and controls is equal to 4.1

Since this is a case-control study, a 2 × 2 table can quickly summarize the information given. Ninety percent of the cases were positive for HPV antibodies, meaning that 315 of the cases were exposed. This leaves 45 cases as unexposed. Similarly, 63% of the controls had a positive HPV test, meaning that 315 controls were exposed while 185 controls were unexposed. Using the information from the table, the odds ratio can be easily calculated and equals the odds of exposure among the cases (315/45) divided by the odds of exposure among the controls (315/185). This ratio equals 4.1.

23. Suppose that one-third of all cervical cancer cases were smokers as were one-third of all controls and smoking status is independent of HPV infection. Is smoking a potential confounder in this study?

a. Yes, the overall odds ratio is still equal to 4.1 after stratification
b. No, the chance of being a smoker among women with cervical cancer is the same as that of being a smoker among women without cervical cancer
c. No, the stratum-specific odds ratios must be equal to indicate confounding
d. Yes, but there is no adequate information on the proportion of smokers in each exposure group to judge the effect on the odds ratio
e. Yes, smoking is highly correlated with HPV infection

The rate of smoking is independent of HPV infection. In order to be a potential confounder, a factor must be related to both exposure and disease. In this instance, the lack of an association between smoking and HPV infection clearly rules out any potential confounding.

24. A case-control study was conducted to determine if an association exists between workers in uranium mines and loss of fertility due to reduced sperm count. A group of 200 men with low sperm count were identified from clinics located in areas with uranium mines. Each selected case was matched with a randomly selected male control on the following factors: race, age, area of residence, and smoking status. What is the purpose of matching?

a. Previous studies have shown that there are racial differences in low sperm count
b. Men of the same age should have the same sperm count level
c. Future analyses using this data can investigate if low sperm count is associated with public drinking water supplies
d. Smoking has no effect on sperm count so it should be the same among cases and controls
e. Matching makes it easier to identify an eligible control for the study

In order to isolate the effect that uranium mining has on sperm counts, the investigators have chosen to create case and control groups with similar distributions of relevant confounders for the study. By matching, the estimated odds ratio should represent the specific contribution of uranium mine exposure to the outcome of the study.

25. The following numbers of matched pairs were reported: 4 matched pairs in which both men worked in a uranium mine, 9 pairs in which the case had mine exposure but the control did not, 2 pairs in which the case had no mine exposure but the control did, and 185 pairs in which neither man had worked in a uranium mine. What is the odds ratio for reduced sperm count among the uranium miners?

a. 4.5
b. 14.4
c. 28.8
d. 41.1
e. 46.3

The matched odds ratio equals the number of discordant pairs in which only the case is exposed divided by the number of discordant pairs in which only the control is exposed. In this example, the matched odds ratio equals 9 divided by 2.

26. A case-control study of the relationship between high-fat diet and diabetes was performed. The results

of the study are shown below, stratified by sex. What is the crude odds ratio for the association between high-fat diet and diabetes in this study?

	Men with High-Fat Diet	Men with Low-Fat Diet	Women with High-Fat Diet	Women with Low-Fat Diet
Diabetes	1,410	1,440	980	640
No diabetes	2,080	1,120	1,160	900

a. 0.5
b. 0.7
c. 1.0
d. 1.2
e. 1.4

The crude odds ratio measures the association between the exposure, high-fat diet, and the outcome, diabetes, in the entire study group. In this instance, combining the information presented for men and women gives an odds ratio of 0.7. This is equal to ratio of the odds of high-fat diet among all persons with diabetes (2390/2080) divided by the odds of a high-fat diet among all persons without diabetes (3240/2020).

27. A case-control study of the relationship between high-fat diet and diabetes was performed. The results of the study are shown below, stratified by gender. What is the odds ratio among men only?

	Men with High-Fat Diet	Men with Low-Fat Diet	Women with High-Fat Diet	Women with Low-Fat Diet
Diabetes	1,410	1,440	980	640
No diabetes	2,080	1,120	1,160	900

a. 0.5
b. 0.7
c. 1.0
d. 1.2
e. 1.4

Among men, this is equal to the ratio of the odds of a high-fat diet among all persons with diabetes (1410/1440) divided by the odds of a high-fat diet among all persons without diabetes (2080/1120).

28. A case-control study of the relationship between high-fat diet and diabetes was performed. The results of the study are shown below, stratified by gender. What is the odds ratio among women only?

	Men with High-Fat Diet	Men with Low-Fat Diet	Women with High-Fat Diet	Women with Low-Fat Diet
Diabetes	1,410	1,440	980	640
No diabetes	2,080	1,120	1,160	900

a. 0.5
b. 0.7
c. 1.0
d. 1.2
e. 1.4

Among women, this is equal to the ratio of the odds of high-fat diet among all persons with diabetes (980/640) divided by the odds of a high-fat diet among all persons without diabetes (1160/900).

29. A case-control study of the relationship between high-fat diet and diabetes was performed. The results of the study are shown below, stratified by gender. Based on the responses above, what is the most appropriate measure of association to present when reporting the results of this study?

	Men with High-Fat Diet	Men with Low-Fat Diet	Women with High-Fat Diet	Women with Low-Fat Diet
Diabetes	1,410	1,440	980	640
No diabetes	2,080	1,120	1,160	900

a. The crude odds ratio
b. The weighted average of the stratum-specific odds ratios
c. The separate stratum-specific odds ratios
d. The odds ratio after adjustment for gender
e. None of the above; an incidence study should be done that better describes the relationship

Since the stratified odds ratios are different between men and women, they must be reported separately. As defined in the text, interaction is indicated when the association between exposure and disease is different in the strata formed by a third variable. In this instance, the effect of a high-fat diet decreases the risk of diabetes for men (odds ratio = 0.7) while a high-fat diet increases the risk of diabetes for women (odds ratio = 1.2). This is a classic indication of interaction between the exposure (high-fat diet) and another factor (gender) that influences disease (diabetes) risk.

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30. A case-control study of the relationship between high-fat diet and diabetes was performed. The results of the study are shown below, stratified by gender. Which of the following is demonstrated by the stratified odds ratio shown Q29

	Men with High-Fat Diet	Men with Low-Fat Diet	Women with High-Fat Diet	Women with Low-Fat Diet
Diabetes	1,410	1,440	980	640
No diabetes	2,080	1,120	1,160	900

a. Confounding by gender
b. Effect modification by gender
c. Selection bias by gender
d. Recall bias by gender
e. Residual confounding by other factors that differ by gender such as exercise activity

The study demonstrates that effect modification is present since the stratified odds ratios are not equivalent. This implies that gender modifies the effect of a high-fat diet on the development of diabetes. By presenting the stratified odds ratios, the researcher presents this possibility when reporting the study results.

31. When incidence density sampling is used in a case-control study, which of the following is an important consideration?

a. A subject identified as a case may later be selected as a control
b. A subject selected as a control may later be selected as a case
c. Control subjects must remain disease free throughout the entire follow-up period
d. Each case is matched to a single control
e. Recall bias is not an issue since exposure is measured prospectively

An incidence density sampling strategy allows an investigator to conduct a case-control study within a defined population. The goal is to include each case subject as they develop the outcome during follow-up time. In some instances, control subjects who do not have the outcome can be matched to each case subject so that controls are selected at the same time as a case is identified. However, one important consideration of this strategy is that each control subject still remains at risk of being an "incident" case during follow-up time and should be included in the case group once the outcome is diagnosed.

32. A recent prospective study on baldness and coronary heart disease (CHD) concluded that there was no association between the two, despite earlier cross-sectional studies which showed that baldness was associated with CHD when the two were determined at the same time in men. Which Bradford-Hill criterion is being tested by the newer study?

a. Validity
b. Temporality
c. Biologic plausibility
d. Analogy
e. Dose-response

The prospective study investigates the development of incident CHD among men classified as bald or not bald. Therefore, exposure must temporally precede the outcome. In the earlier study, men were classified as bald or not bald at the time of their CHD diagnosis. Since CHD may have a long latency period, it may be possible that baldness developed subsequent to CHD. Therefore, only a prospective study can address this Bradford-Hill criterion.

33. A study examined the relation between use of estrogen replacement therapy (ERT) and ovarian cancer mortality using a prospective design. Of 24,231 eligible women, none had a prior history of cancer, hysterectomy, or ovarian surgery at enrollment in 1982. During 12 years of follow-up, 44 deaths from ovarian cancer occurred. In the published results, the authors note that 12,543 were excluded from the original cohort due to missing information for prior history variables. Which of the following is of greatest concern when interpreting the study results?

a. Selection bias
b. Information bias
c. Confounding
d. Effect modification
e. Precision

Since nearly one-half of eligible subjects were excluded from the study, the accuracy of the measure of association between ERT and ovarian cancer mortality may be significantly biased. This bias could reduce the validity of the measure of association

34. A study examined the relation between use of estrogen replacement therapy (ERT) and ovarian cancer mortality using a prospective design. Of 24,231 eligible women, none had a prior history of cancer, hysterectomy, or ovarian surgery at enrollment in

1982. During 12 years of follow-up, 44 deaths from ovarian cancer occurred. In the published results, the authors note that 12,543 were excluded from the original cohort due to missing information for prior history variables.

Age at menopause is a potential factor associated with use of ERT. The study investigators created three categories for age at menopause: less than 45 years, 46 through 54 years, and 55 years or more. After stratifying on age at menopause, the researchers reported relative risks of 0.97, 1.00 (referent), and 0.93 for each age group, respectively. Which of the following is true?

a. Age at menopause may modify the effect of ERT on ovarian cancer mortality
b. The odds ratios are biased toward the null due to information bias
c. The referent group of women who had menopause between ages 46 and 54 years is incorrectly chosen
d. Age at menopause is unlikely to be a strong confounder of the relationship between ERT use and ovarian cancer mortality
e. The investigators need to analyze age as a continuous measure of years since creating categories may introduce misclassification

Age at menopause is unlikely to be a confounder of the relationship between ERT use and ovarian cancer mortality since the stratum-specific relative risks are nearly equivalent and are close to the null value of 1.0.

35. A case-control study was conducted to assess whether occupational radiation exposure among men was associated with Down syndrome in their children. The investigators matched cases and controls on age of the mother at childbirth by 5-year categories. Why was this done?

a. To minimize selection bias due to cases having older mothers
b. To minimize information bias about maternal age
c. To adjust for potential confounding by maternal age
d. To measure effect modification by increasing maternal age categories
e. To exclude children born to younger parents

Older maternal age is definitely associated with increased likelihood of Down syndrome in children. By matching on maternal age, the investigators reduce the role that maternal age has on the outcome.

36. A case-control study was conducted to assess whether occupational radiation exposure among men was associated with Down syndrome in their children. The investigators matched cases and controls on age of the mother at childbirth by 5-year categories. When possible, information on paternal radiation exposure was taken from employment records rather than from subject interviews. Why was this done?

a. To minimize detection bias for cases
b. To minimize differential misclassification of exposure
c. To remove selection bias of non-radiation exposed fathers
d. To provide dose-response information
e. To minimize recall bias of exposure

In a case-control study of a rare outcome, cases are more likely to recall exposures that they believe may have contributed to the outcome. In this instance, paternal radiation exposure may be recalled much more precisely by fathers of affected children when compared to fathers of nonaffected children.

37. An epidemiologist was interested in determining whether aspirin was associated with an increased risk of gastrointestinal (GI) bleeding. They relied on primary physicians to identify 600 patients at a hospital who were taking a daily dose of aspirin and 600 other patients who were not taking aspirin. Subjects were followed for 1 year to detect any occurrences of GI bleeding. Due to publicity about the risk of bleeding associated with aspirin, primary physicians treating patients at the hospital followed their patients who were taking aspirin more closely than those who were unexposed subjects. Which of the following describes the impact that this may have on the epidemiologist's study?

a. Would result in nondifferential classification of exposure
b. Would result in differential classification of exposure
c. Would result in nondifferential classification of outcome
d. Would result in differential classification of outcome
e. Would introduce recall bias

Since the publicity concerning aspirin use and GI bleeding informed primary physicians that patients taking aspirin may be at increased risk of this outcome,

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they would be more likely to diagnose GI bleeding among their patients who were exposed. This differential classification of the outcome by exposure group would lead to biased results of the epidemiologist's study.

38. An epidemiologist was interested in determining whether aspirin was associated with an increased risk of gastrointestinal (GI) bleeding. They relied on primary physicians to identify 600 patients at a hospital who were taking a daily dose of aspirin and 600 other patients who were not taking aspirin. Subjects were followed for 1 year to detect any occurrences of GI bleeding. Due to publicity about the risk of bleeding associated with aspirin, primary physicians treating patients at the hospital followed their patients who were taking aspirin more closely than those who were unexposed subjects.

Suppose that the study was repeated with a second physician who was responsible for verifying a diagnosis of GI bleeding in the patients. This physician was informed that all patients were using aspirin. If the likelihood of diagnosing the outcome among unexposed subjects was increased while all other diagnostic probabilities remained the same, what impact would this have on the bias?

a. The bias would be eliminated
b. The bias would change the risk estimate so that the association between GI bleeding and aspirin use would be reversed
c. The bias would decrease toward the null
d. The bias would increase the risk estimate
e. None of the above

By increasing the likelihood of diagnosing GI bleeding in nonexposed subjects, the number of outcomes would increase in the nonexposed group. This increase would dilute the effect of the association between aspirin use and GI bleeding noted in the exposed subjects so that the risk measure would be closer to a null value of 1.0 depending on the strength of the true measure of effect.

39. Matching is employed in a case-control study in order to ensure that:

a. Variables associated with the outcome under study are controlled for in both the case and control groups
b. The eligible sample size is increased for case and control selection
c. Recall bias is minimized between cases and controls
d. The study investigators can estimate measures of association between matching
e. The follow-up time for the study is decreased

Matching is done in case-control studies since a major concern is that the two groups may differ by some variable other than the exposure under investigation. By matching cases and controls on these variables that influence both exposure and outcome, the investigator seeks to control the effect of these variables by making their distributions identical in the two study groups.

40. The effect of exposure to high-density automobile traffic either as a bicyclist or pedestrian was compared to minimal or no exposure to automobile traffic. It is hypothesized that direct exposure to automobile traffic has an effect on acute myocardial infarction (MI). This association was studied with 500 incident cases of MI diagnosed in the emergency rooms of several hospitals and compared to 1,000 other subjects who visited the same emergency rooms for reasons other than cardiovascular and respiratory diseases. All subjects were asked to report the amount of time that they spent exposed to high-density traffic over the past month prior to their hospital visit.

What type of study design is this?

a. Cross-sectional
b. Case-control
c. Non-concurrent cohort
d. Concurrent cohort
e. Randomized clinical trial

The study design relies on hospital-based recruitment of cases (persons with an MI) and controls (other patients in the emergency room who did not have cardiovascular and respiratory diseases which may be associated with air pollution). The exposure under investigation is a time-dependent measure of exposure to high-density automobile traffic in the days preceding the emergency room visit.

41. The effect of exposure to high-density automobile traffic either as a bicyclist or pedestrian was compared to minimal or no exposure to automobile traffic. It is hypothesized that direct exposure to automobile traffic has an effect on acute myocardial infarction (MI). This association was studied with 500 incident cases of MI diagnosed in the emergency rooms of several hospitals and compared to 1,000 other subjects who visited the same

emergency rooms for reasons other than cardiovascular and respiratory diseases. All subjects were asked to report the amount of time that they spent exposed to high-density traffic over the past month prior to their hospital visit.

After completing the recruitment, the investigators compiled their data in the following table:

	EXPOSED TO HIGH-DENSITY AUTOMOBILE TRAFFIC		
Disease Status	**Frequently (Daily)**	**Rarely (Less Than daily)**	**Never**
Acute MI	120	240	140
Other ER visit	440	300	260

Using the appropriate measure of association, as compared to the group with no traffic exposure, which of the following is a true statement concerning MI?

- **a.** The estimated risk of MI is identical for those exposed to automobile traffic either daily or rarely
- **b. The estimated risk of MI was higher for those exposed rarely than for those exposed daily to automobile traffic**
- **c.** The estimated risk was higher for those exposed daily rather than for those exposed rarely to automobile traffic
- **d.** Neither daily nor rare exposure to automobile traffic was associated with an increased risk for MI
- **e.** None of the above

The estimated odds ratio for daily exposure to high-density automobile traffic is 0.5 while the estimated odds ratio for rare exposure is 1.5. It is evident that the estimated risk of MI was higher among those with rare exposure to automobile traffic.

42. The effect of exposure to high-density automobile traffic either as a bicyclist or pedestrian was compared to minimal or no exposure to automobile traffic. It is hypothesized that direct exposure to automobile traffic has an effect on acute myocardial infarction (MI). This association was studied with 500 incident cases of MI diagnosed in the emergency rooms of several hospitals and compared to 1,000 other subjects who visited the same emergency rooms for reasons other than cardiovascular and respiratory diseases. All subjects were asked to report the amount of time that they spent exposed to high-density traffic over the past month prior to their hospital visit.

Which of the following may explain the reason for the observed association?

- **a.** Effect modification by time spent exposed to automobile traffic
- **b.** Confounding by time spent exposed to automobile traffic
- **c.** Recall bias among those with daily exposure to automobile traffic
- **d.** Selection bias to avoid automobile traffic among those predisposed to MI
- **e. Confounding by exercise level for those with daily exposure to automobile traffic**

Since the investigators measured exposure to automobile traffic through direct contact either as a bicyclist or pedestrian, there is likely to be confounding by exercise level between the groups. Persons who either bike or walk daily are more likely to be fit than those who avoid these activities. Since lack of fitness is a risk factor for an acute MI, it is likely to influence the measure of association in this study.

43. Which of the following is an advantage of the case-control study design?

- **a.** Recall bias is avoided
- **b.** Little to no bias when assessing the outcome of interest
- **c. It is possible to study more than one exposure**
- **d.** It is possible to study more than one disease outcome
- **e.** The study design is useful for studying rare exposures

Case-control studies start with a definition of those with a specific disease outcome, i.e., cases, and compare these persons to those without the outcome of interest, i.e., controls. A wide range of exposures can be included for assessment in the study groups and can be evaluated using the preferred measure of association, the odds ratio.

44. A large case-control study using multiple recruitment centers was conducted comparing 2,987 lung smoker cases to 3,013 other hospitalized persons selected as controls. One objective was to study the association between occupational exposure to chemicals and lung cancer. After compiling the data, the investigators noted that 90% of persons with lung cancer were smokers while 67% of the controls were smokers. The most practical and

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efficient way to eliminate differences between the cases and controls with regard to smoking would be to:

a. Repeat the selection of the controls matching on smoking status
b. Calculate incidence rates for lung cancer by smoking status
c. Exclude smokers from the study
d. Classify subjects according to smoking status and compare occupational chemical exposures by each stratum of smoking
e. Ignore smoking classification and report unadjusted risk estimates

Since smoking is highly prevalent among both groups and there are sufficient numbers of cases and controls, the most efficient method would be to report stratified risk estimates based on smoking history. Smoking is highly associated with lung cancer as well as other health end points and cannot be ignored.

45. An investigator is interested in studying the adverse effects of exposure to toxic metals on neurologic diseases such as Alzheimer disease. In assessing this risk, all of the following are important considerations for a prospective study design except:

a. The need to recruit a large sample size
b. The possible bias introduced by lifetime exposure assessments
c. The difficulty in finding sufficient numbers of persons with neurologic disease in whom past metal exposures could be measured at the beginning of the study
d. The likelihood that persons with exposure to toxic metals may be more likely to receive a diagnosis of neurologic disease
e. The possibility that exposure to toxic metals may change during the follow-up period

Since the study is being designed as a concurrent cohort study, there is no need to identify persons with existing disease at the beginning of the study. If there are sufficiently large numbers of exposed and unexposed persons recruited at the start of the study, then there should be adequate numbers of events occurring during follow-up.

46. A history of dietary supplement with calcium was recorded among 10,000 women over the age of 50. The women were followed for 2 years to determine if they experienced hip fracture. Calcium supplementation was reported by 31% of women who experienced hip fracture and by 46% of all other women. In a case-control study with equal numbers of cases and controls, what is the number of women with a hip fracture who are not taking calcium supplements?

a. 1,550
b. 2,300
c. 2,700
d. 3,450
e. 5,000

This is found by completing a 2 × 2 table for the study. For the 5,000 women who are considered cases, there are 1,550 who were exposed to calcium supplements. This leaves 3,450 who were not taking supplements (69% of the cases).

47. A history of dietary supplement with calcium was recorded among 10,000 women over the age of 50. The women were followed for 2 years to determine if they experienced hip fracture. Calcium supplementation was reported by 31% of women who experienced hip fracture and by 46% of all other women. What are the odds of a hip fracture among women who are taking calcium supplements?

a. 0.25
b. 0.45
c. 0.67
d. 0.85
e. 1.28

The odds of the outcome among those exposed is found by dividing the number of exposed cases by the number of exposed controls. After completing a 2 × 2 table, this equals 1,550 divided by 2,300. Therefore the odds of hip fracture among those taking calcium supplements is 0.67.

48. A history of dietary supplement with calcium was recorded among 10,000 women over the age of 50. The women were followed for 2 years to determine if they experienced hip fracture. Calcium supplementation was reported by 31% of women who experienced hip fracture and by 46% of all other women. What is the measure of association between calcium supplementation and hip fracture?

a. Relative risk=0.72
b. Relative risk=1.39
c. Odds ratio=0.53
d. Odds ratio=1.89
e. None of the above

Since this is a case-control study with 5,000 cases and 5,000 controls, a 2 × 2 table is completed using the exposure probability listed above. For this study, that results in an odds ratio equal to (1550/3450) divided by (2300/2700), or 0.53. Therefore, the odds of a hip fracture in women taking calcium supplements is approximately one-half that of women not taking supplements.

49. In a study of 100 cases of colon cancer in women, there were 200 age- and race-matched controls. The suspected etiologic factor was higher-than-average consumption of red meat. The absolute risk of colon cancer in persons with this level of consumption is:

- **a.** 25%
- **b.** 50%
- **c.** 67%
- **d.** 100%
- **e. Cannot be calculated**

In a case-control study in which cases and controls are selected into the study, a measure of absolute disease risk such as incidence cannot be calculated. In order to calculate absolute risk, the investigators would need to start with a concurrent cohort study in which persons are classified as exposed based on their level of meat consumption. After a suitable follow-up period, the incidence of colon cancer in each group could be used to estimate absolute risk.

50. Why are controls needed in a case-control study?

- **a.** They may be followed for development of the outcome of interest
- **b.** They are less likely to have recall bias issues
- **c.** They increase the size of the study so that risk estimates are significant
- **d.** They do not have the exposure of interest and allow for the estimation of disease frequency among the unexposed
- **e. They do not have the outcome of interest and allow for estimation of exposure frequency among those without the disease**

A case-control study is the most convenient way to test the association between an exposure and a disease outcome. By comparing the proportions of exposure between persons with and without the disease of interest, an estimate of risk can be developed that expresses this relationship.

51. When is odds ratio obtained in a case-control study a reliable approximation of the relative risk for the general population?

- **a.** The exposure distribution among cases is representative of all persons with disease
- **b.** The exposure opportunity for controls is equivalent to the distribution of exposure opportunities for the population without the disease
- **c.** When the disease under investigation is rare in the population
- **d.** a and b only
- **e. All of the above**

In a case-control study, the odds ratio is the measure of association most often estimated. In order for this measure to be an approximate estimate of the relative risk, all three conditions must be met. In essence, these conditions imply that both cases and controls are representative of the overall population from which they are sampled and that the rarity of disease occurrence indicates that most persons are not at increased risk for the disease.

52. In a published epidemiologic study investigating infertility related to sexually transmitted diseases (STD), the authors state that 5% of identified cases refused enrollment, 10% of identified cases were lost to follow-up prior to data collection, and 10% of interviewed cases had missing data for one or more key variables describing exposure. Based on this information, which of the following statements is most likely to be true?

- **a.** Some degree of bias is inevitable
- **b. There is a potential for selection bias which could be differential with respect to cases and controls**
- **c.** There is a potential for selection bias which could be nondifferential with respect to cases and controls
- **d.** There is likely to be nondifferential misclassification of the outcome
- **e.** There is no selection bias; however, confounding may be introduced by missing variables

The loss of cases for all of the listed reasons indicates that the enrolled cases may not be representative of all persons with infertility under investigation. Therefore, this selection issue would introduce bias when estimating the measure of association between STD history and case status.

53. In a published epidemiologic study investigating infertility related to sexually transmitted diseases (STD), the authors state that 5% of identified cases refused enrollment, 10% of identified cases were

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lost to follow-up prior to data collection, and 10% of interviewed cases had missing data for one or more key variables describing exposure. After data were gathered for the study, the investigators decided to restrict the analysis to women only, rather than including both men and women in the study. Assuming that sex is a confounder of the exposure–disease relationship under investigation, this decision would have which of the following effects?

a. Increase internal validity
b. Increase potential confounding
c. Enable the study of sex as an effect modifier
d. Increase the likelihood of a statistically significant result
e. Introduce selection bias based on sex

Assuming that sex is a confounder of STD history and infertility, then restricting the analysis to women only would reduce the influence of this variable. This would increase the validity of the results of the study; however, any inferences made from the study estimate would be limited to conclusions about the exposure–disease association in women only.

54. In a published epidemiologic study investigating infertility related to sexually transmitted diseases (STD), the authors state that 5% of identified cases refused enrollment, 10% of identified cases were lost to follow-up prior to data collection, and 10% of interviewed cases had missing data for one or more key variables describing exposure.

In the primary analysis of the study, the investigators measured exposure as a dichotomous variable (any history of STD compared to no history of STD). In subsequent analyses, the investigators looked at the relationship between specific STDs and infertility. They noted the following measures of association: for past history of gonorrhea, the odds ratio was 2.4 with a 95% confidence interval of 1.3 to 4.4. For past history of chlamydia, the odds ratio was 1.8 with a 95% confidence interval from 1.2 to 2.1. These results indicate that:

a. There is effect modification by STD type since the odds ratios are different from each other
b. There is confounding by STD type since the odds ratios are different from each other
c. The odds ratio for chlamydia is more precise than the odds ratio for gonorrhea
d. The odds ratio for chlamydia is biased toward the null
e. Neither odds ratio is a reliable approximation of the relative risk

When estimating measures of association, the 95% confidence interval is generally used to express the range of the measure under the null hypothesis. The interval covered by the confidence interval is smaller when sample sizes are large such that the potential values of the odds ratio relative to the null hypothesis are contained in a more limited range. In this instance, there is inadequate information to judge the correctness of the other responses such that c is the best answer.

55. An investigator analyzing the results of a clinical trial, then applying the "intention to treat" rule means that which type of bias is most likely to result?

a. Misclassification bias
b. Confounding
c. Effect modification
d. Selection bias
e. No bias would result

"Intention to treat" indicates that the analysis of the data is conducted such that the subject's assigned treatment group is retained when estimating the measure of association. For example, this would mean that a subject assigned to the placebo group would be categorized with this "exposure" even if they later took the drug given to the "exposed" group. This assumption has several advantages when information is limited about compliance; however, it is probable that misclassification of exposure could result when applying this rule.

56. Investigators wanted to know if some military personnel are more error prone than others and would be a poor risk for training as a pilot. A study was done in which individuals who had injuries during basic training were compared to individuals who had not had an injury during training. Both groups were asked to recall episodes during childhood when they had had accidents that resulted in an injury. The individuals with a training injury reported more incidents during childhood when they had an injury. Therefore, the military command concluded that some persons are more likely to be error prone and that individuals with a childhood injury should be excluded from pilot training.

One commanding officer disagreed with this conclusion. He asked the investigators to design a second study in which all individuals were asked about childhood injuries prior to the start of basic training. The group who reported having a childhood injury was compared

to the group who had not had a childhood injury to determine which group had a higher rate of injuries during basic training. At the end of follow-up, there was no difference in the rate of injuries experienced by each group.

What type of design was used for the first study?

a. Cross-sectional
b. Case-control
c. Non-concurrent cohort
d. Concurrent cohort
e. Randomized clinical trial

The first study was retrospective and had two groups: those who had a training injury ("cases") compared to those who did not have a training injury ("controls"). Exposure was assessed after case status and it is highly likely that both investigators and subjects were aware of case status since the subjects had recently finished basic training.

57. Investigators wanted to know if some military personnel are more error prone than others and would be a poor risk for training as a pilot. A study was done in which individuals who had injuries during basic training were compared to individuals who had not had an injury during training. Both groups were asked to recall episodes during childhood when they had had accidents that resulted in an injury. The individuals with a training injury reported more incidents during childhood when they had an injury. Therefore, the military command concluded that some persons are more likely to be error prone and that individuals with a childhood injury should be excluded from pilot training.

One commanding officer disagreed with this conclusion. He asked the investigators to design a second study in which all individuals were asked about childhood injuries prior to the start of basic training. The group who reported having a childhood injury was compared to the group who had not had a childhood injury to determine which group had a higher rate of injuries during basic training. At the end of follow-up, there was no difference in the rate of injuries experienced by each group.

What type of study design was used for the second study?

a. Cross-sectional
b. Case-control
c. Non-concurrent cohort
d. Concurrent cohort
e. Randomized clinical trial

The second study was prospective and had two groups: those who reported childhood injury ("exposed") compared to those who did not have a childhood injury ("nonexposed"). Outcome status was assessed after follow-up through basic training though no information is given that investigators were blinded to exposure status when determining whether or not a training-related injury occurred.

58. Investigators wanted to know if some military personnel are more error prone than others and would be a poor risk for training as a pilot. A study was done in which individuals who had injuries during basic training were compared to individuals who had not had an injury during training. Both groups were asked to recall episodes during childhood when they had had accidents that resulted in an injury. The individuals with a training injury reported more incidents during childhood when they had an injury. Therefore, the military command concluded that some persons are more likely to be error prone and that individuals with a childhood injury should be excluded from pilot training.

One commanding officer disagreed with this conclusion. He asked the investigators to design a second study in which all individuals were asked about childhood injuries prior to the start of basic training. The group who reported having a childhood injury was compared to the group who had not had a childhood injury to determine which group had a higher rate of injuries during basic training. At the end of follow-up, there was no difference in the rate of injuries experienced by each group.

Which study better tests the hypothesis that there is a relationship between childhood injury and subsequent injury during basic training?

a. Case-control study
b. Concurrent cohort study
c. Both studies adequately test the hypothesis
d. Neither study adequately tests the hypothesis
e. A randomized trial should be performed to adequately test the hypothesis

Since the prospective study establishes a baseline categorization of exposure prior to follow-up for the outcome, this study is a better test of the hypothesis that childhood injury is related to training injury. Given that there may be significant differences in the definition and determinations of injury, it is not surprising that the second study reports no association between the two.

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59. Investigators wanted to know if some military personnel are more error prone than others and would be a poor risk for training as a pilot. A study was done in which individuals who had injuries during basic training were compared to individuals who had not had an injury during training. Both groups were asked to recall episodes during childhood when they had had accidents that resulted in an injury. The individuals with a training injury reported more incidents during childhood when they had an injury. Therefore, the military command concluded that some persons are more likely to be error prone and that individuals with a childhood injury should be excluded from pilot training. One commanding officer disagreed with this conclusion. He asked the investigators to design a second study in which all individuals were asked about childhood injuries prior to the start of basic training. The group who reported having a childhood injury was compared to the group who had not had a childhood injury to determine which group had a higher rate of injuries during basic training. At the end of follow-up, there was no difference in the rate of injuries experienced by each group.

Which of the following may explain why the two studies observed different results concerning the association between childhood injury and training injury?

- **a.** Confounding by age
- **b.** Effect modification by type of training
- **c.** Misclassification bias toward the null in the concurrent cohort study
- **d.** Potential selection bias in the case-control study
- **e. Potential recall bias in the case-control study**

The case-control study reports a positive association between childhood injury and training injury. Since cases were defined by having experienced a training-related injury, it is more likely that they would recall episodes of childhood injury relative to the controls due to their recent experience.

60. A matched case-control study of sunscreen use during childhood and melanoma results in an odds ratio of 1.0. Cases of melanoma were matched by sex and race to controls who were identified by random digit dialing. What is the most likely explanation for the study's null finding?

- **a.** Selection bias for controls
- **b.** Confounding by age
- **c. Information bias concerning past sunscreen use**
- **d.** Lack of a true association between childhood sunscreen use and melanoma
- **e.** Inadequate sample size

It is likely that persons are unable to recall childhood sunscreen use. This would decrease the proportion of exposure for both groups and lead to a bias toward the null that could mask the protective association between childhood sunscreen use and melanoma.

61. Among patients with liver cancer, current alcohol drinkers have a worse prognosis for survival than nondrinkers. What would be the impact on the odds ratio for a case-control study of current alcohol use and liver cancer mortality if prevalent cases were included with incident cases of the cancer?

- **a.** Increase the odds ratio when prevalent cases are included
- **b. Decrease the odds ratio when prevalent cases are included**
- **c.** There would be no difference in the odds ratio estimated by either study
- **d.** The odds ratio would be affected by differential selection bias
- **e.** The odds ratio would be a better approximation of the relative risk

Prevalent cases of liver cancer would most likely change their drinking behavior following a diagnosis of liver cancer. This would reduce the odds ratio estimate since fewer cases would report being exposed, while there would be no change in the proportion of controls who reported current drinking.

62. In a cohort study, the reported relative risk was 2.0; however, the investigators concluded that the study likely had a bias away from the null hypothesis, but they concluded that an association did exist between the exposure and the outcome. The true relative risk is most likely:

- **a.** 0.5
- **b.** 1.0
- **c. 1.5**
- **d.** 2.0
- **e.** 4.0

Since the investigators concluded that a valid positive association existed between exposure and outcome, the true relative risk must be greater than 1.0. However, the reported relative risk was biased away from the null hypothesis meaning that it was greater than the true measure of association. This would imply that 1.5 is the best estimate for the relative risk.

63. In a case-control study of maternal cigarette smoking as a risk factor for low birth weight, the investigators concluded that mothers of children with low birth weight were more likely to report smoking during pregnancy relative to mothers of children with normal birth weight. The reporting error most likely caused the odds ratio to:

a. Increase above the true value
b. Decrease below the true value but remain positive
c. There was no change in the odds ratio from the true value
d. Change direction such that smoking prevented low birth weight
e. Equal the relative risk

Since exposure was more likely to be reported by mothers of children with low birth weight, the study is also more likely to find an association between smoking and low birth weight due to the increased likelihood of cases being classified as exposed.

64. In a case-control study of obesity and adult-onset asthma, controls are matched to cases on the basis of race and gender. This approach to selection is intended to decrease the influence of which type of bias?

a. Selection bias
b. Ecologic fallacy
c. Information bias
d. Misclassification
e. Confounding

Since race and gender are likely to be associated with both the exposure (obesity) and outcome (asthma), they could bias the estimated measure of association if not controlled for. Matching is the most efficient way to control for these potential confounders.

65. In a case-control study of computer display exposure and glaucoma, cases and controls were also asked about television watching habits. Errors in recall of exposure to video screens occurred with equal frequency among cases and controls. Which one of the following biases likely occurred?

a. Selection bias
b. Ecologic fallacy
c. Nondifferential misclassification
d. Differential misclassification
e. Confounding

Since the investigators concluded that recall errors were equally likely in cases and controls, then the bias would be nondifferential with respect to case status.

66. In a case-control study of computer display exposure and glaucoma, cases and controls were also asked about television watching habits. Errors in recall of exposure to video screens occurred with equal frequency among cases and controls. What is the most likely effect of this bias on the measure of association reported by the study?

a. Underestimated the true relationship
b. Overestimated the true relationship
c. No effect on the estimate
d. Cannot be determined because the bias is differential
e. The estimate is valid if adjusted for confounders

Nondifferential misclassification tends to result in an underestimation of the true effect. This is more commonly known as bias toward the null since any true association between exposure and outcome is diluted by the equal likelihood of incorrect exposure recall by both cases and controls.

67. In a case-control study of computer display exposure and glaucoma, cases and controls were also asked about television watching habits. Errors in recall of exposure to video screens occurred with equal frequency among cases and controls. Which of the following methods for adjusting for confounding by age is most likely to affect the generalizability of the study findings?

a. Randomization
b. Restriction of study subjects to those less than 50 years old
c. Stratification to several age groups
d. Matching by age plus or minus 5 years
e. Adjustment for age in a regression analysis

The findings of a study can be generalizable when the study is representative of the entire population at risk. By restricting the study to persons less than 50 years of age, no conclusions can be made concerning the risk for persons older than this. Since glaucoma tends to be a disease of older persons, the generalizability of the study may be reduced by this restriction.

68. In a cohort study of occupational exposure to a chemical and subsequent incidence of bladder cancer, all workers who smoked were more likely to die of other causes before bladder cancer was diagnosed. What was the effect of this premature mortality on the measure of association reported by the study?

a. Underestimated the true relationship
b. Overestimated the true relationship

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c. No effect on the estimate
d. Cannot be determined because the bias is differential
e. The estimate is valid if adjusted for smoking

Since there is no indication that smoking differed by exposure status to the chemical of interest, it is likely that premature mortality reduced the number of bladder cancer cases in both exposed and nonexposed groups. Since this process is nondifferential, the study estimate would be biased toward the null and would underestimate the true relationship.

69. Which of the following statements about person-years is not true?
a. It allows for different lengths of follow-up time among study subjects
b. It is a valid denominator for estimates of risk for individuals
c. 20 persons followed for 5 years each contribute the same amount of person-years as 200 subjects followed for 6 months each
d. It is the amount of time that a subject was without the outcome
e. Person-years are not calculated for time during a study when outcome status is not known for subjects lost to follow-up

Person-years are a useful way to measure the rate at which events occur in a group of persons followed for different periods. However, the risk in any person-year may not be the same for different individuals. This may be true when evaluating persons for a disease with a long latency period such as cancer. A study that includes 5,000 persons for 2 years may not have an equivalent underlying risk as a study of 1,000 persons followed for 10 years.

CHAPTERS 16–20 REVIEW QUESTIONS (30 QUESTIONS)

1. A large company institutes a new wellness program aimed at improving the health of its 50,000 employees. As a part of the program, all employees are given physical examinations and screening tests. One of the tests given to male employees is the prostate specific antigen (PSA) test with all employees testing positive being referred to their private physician for a thorough examination involving the standard test, a digital rectal examination (DRE). What will happen to the apparent incidence rate of prostate cancer in the company during the first year of this program?
a. Incidence rate will stay the same
b. Incidence rate will increase
c. Incidence rate will decrease
d. Incidence rate will equal the general population rate
e. Not enough information is available

Given that prostate cancer is one of the most common cancers of men, it is highly prevalent but often undiagnosed. Any effort to intensify screening for prostate cancer will increase the number of cases found in a local population.

2. A large company institutes a new wellness program aimed at improving the health of its 50,000 employees. As a part of the program, all employees are given physical examinations and screening tests. One of the tests given to male employees is the prostate specific antigen (PSA) test with all employees testing positive being referred to their private physician for a thorough examination involving the standard test, a digital rectal examination (DRE). On referral to their private physician, approximately 30% of men with a positive PSA are found to be negative for prostate cancer following the DRE. What is the sensitivity of the PSA test if DRE is assumed to be the gold standard?
a. 30%
b. 70%
c. 0.3 times the sensitivity of DRE
d. 0.7 times the sensitivity of DRE
e. Cannot be calculated due to missing information

Since only men with a positive PSA test are sent for the DRE, those who test negative on the PSA are not available for further testing to determine the number of false negatives from the PSA screening. The lack of this information means that the sensitivity of the test cannot be calculated.

3. The following table shows data describing age-standardized incidence rates for cervical and breast

cancer among Irish women living in Ireland, Irish immigrants to the United States, and daughters of Irish immigrants in the United States. The rates are reported for two age categories: adult women younger than 40 years of age and older than 40 years of age. Which cancer appears to be determined primarily by environmental factors?

Cancers per 100,000 Women	Women in Ireland	Irish Immigrants	Daughters of Irish Immigrants
Cervical <40 yrs	6.8	8.4	10.2
Cervical >40 yrs	8.2	9.7	12.2
Breast <40 yrs	42.0	45.0	44.1
Breast >40 yrs	75.0	88.0	84.2

a. Cervical
b. Breast
c. Both
d. Neither
e. Cannot be determined due to confounding by area of residence

Cervical cancer is one of the most common cancers of women. The most important risk factor is infection with human papillomavirus (HPV). Since the incidence rates for the cancer varies for each group in both age categories, this cancer is determined primarily by environmental factors.

4. The following table shows data describing age-standardized incidence rates for cervical and breast cancer among Irish women living in Ireland, Irish immigrants to the United States, and daughters of Irish immigrants in the United States. The rates are reported for two age categories: adult women less than 40 years of age and greater than 40 years of age. Which cancer appears to be determined primarily by genetic factors?

Cancers per 100,000 Women	Women in Ireland	Irish Immigrants	Daughters of Irish Immigrants
Cervical <40 yrs	6.8	8.4	10.2
Cervical >40 yrs	8.2	9.7	12.2
Breast <40 yrs	42.0	45.0	44.1
Breast >40 yrs	75.0	88.0	84.2

a. Cervical
b. Breast
c. Both
d. Neither
e. Cannot be determined due to confounding by age

Both cancers are very common in women. Though a proportion of breast cancer is attributable to genetic factors especially in women less than 40 years of age, the incidence rates reported here show that it is not very different between subgroups of the Irish female population. Primarily environmental but also genetic factors contribute to breast cancer incidence with age-related risk factors.

5. The following table shows data describing age-standardized incidence rates for cervical and breast cancer among Irish women living in Ireland, Irish immigrants to the United States, and daughters of Irish immigrants in the United States. The rates are reported for two age categories: adult women less than 40 years of age and greater than 40 years of age. Among women less than 40 years of age, what is the relative risk for cervical cancer comparing daughters of Irish immigrants to women in Ireland?

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Cancers per 100,000 Women	Women in Ireland	Irish Immigrants	Daughters of Irish Immigrants
Cervical <40 yrs	6.8	8.4	10.2
Cervical >40 yrs	8.2	9.7	12.2
Breast <40 yrs	42.0	45.0	44.1
Breast >40 yrs	75.0	88.0	84.2

a. 1.50
b. 1.55
c. 1.64
d. 2.70
e. Cannot be calculated with the information provided

The relative risk is equal to the incidence rate in daughters of Irish immigrants divided by the incidence rate for women in Ireland. In these data, the relative risk equals 10.2 divided by 6.8.

6. The following table shows data describing age-standardized incidence rates for cervical and breast cancer among Irish women living in Ireland, Irish immigrants to the United States, and daughters of Irish immigrants in the United States. The rates are reported for two age categories: adult women less than 40 years of age and greater than 40 years of age. What is the percentage of cervical cancer risk in Irish women under 40 years of age that is attributable to moving to the United States?

Cancers per 100,000 Women	Women in Ireland	Irish Immigrants	Daughters of Irish Immigrants
Cervical <40 yrs	6.8	8.4	10.2
Cervical >40 yrs	8.2	9.7	12.2
Breast <40 yrs	42.0	45.0	44.1
Breast >40 yrs	75.0	88.0	84.2

a. 12%
b. 24%
c. 56%
d. 100%
e. Cannot be calculated with the information provided

This question asks for the percent attributable risk which is equal to the incidence in the "exposed" group (Irish immigrants to the United States) less the incidence in the "nonexposed" group (Irish women in Ireland) divided by the incidence in the nonexposed group. This calculation represents the proportion of cervical cancer risk that can be attributed to the risk factor of immigration to the United States.

7. The following table shows data describing age-standardized incidence rates for cervical and breast cancer among Irish women living in Ireland, Irish immigrants to the United States, and daughters of Irish immigrants in the United States. The rates are reported for two age categories: adult women less than 40 years of age and greater than 40 years of age. Which cancer has a greater risk after the onset of menopause?

Cancers per 100,000 Women	Women in Ireland	Irish Immigrants	Daughters of Irish Immigrants
Cervical <40 yrs	6.8	8.4	10.2
Cervical >40 yrs	8.2	9.7	12.2
Breast <40 yrs	42.0	45.0	44.1
Breast >40 yrs	75.0	88.0	84.2

a. Cervical
b. **Breast**
c. Both
d. Neither
e. Cannot be calculated with the information provided

The relative risks for cervical cancer among older women (>40 years) compared to younger women are approximately 1.2 for each subgroup. The relative risks for breast cancer for this comparison are approximately 1.9. Therefore, the risk of breast cancer is more substantial with the onset of menopause as denoted by increasing age.

8. The data in the table below are from a case-control study of a genetic factor associated with neurologic disease. Cases are newly diagnosed persons with the rare neurologic condition, and population controls were used for comparison. Investigators have hypothesized that a single point mutation in a gene on the 10th chromosome is strongly related to the disease. In the table, subjects who are homozygous for the mutation are denoted as m/m; subjects with only one mutated gene (heterozygous for the mutation) are denoted as A/m; and subjects with two normal alleles (homozygous for the absence of the mutation) are denoted as A/A. The unexposed category for the study is the A/A genotype. The neurologic condition is thought to be autosomal dominant with respect to the gene; therefore, one copy of the m allele should induce the development of the condition. What is the odds ratio for subjects with at least one copy of the mutant allele?

Status	m/m	A/m	A/A
Case	354	22	40
Control	0	48	385

a. 0.01
b. 0.5
c. 1.0
d. **75.4**
e. Cannot be calculated due to zero controls in one cell

The odds ratio should be calculated after combining all persons with at least one copy of the mutation. This results in 376 exposed cases, 48 exposed controls, 40 nonexposed cases, and 385 nonexposed controls. The odds ratio equals (376 divided by 48) divided by (48 divided by 385). This calculation equals 75.4.

9. The data in the table in Q8 are from a case-control study of a genetic factor associated with neurologic disease. Cases are newly diagnosed persons with the rare neurologic condition, and population controls were used for comparison. Investigators have hypothesized that a single point mutation in a gene on the 10th chromosome is strongly related to the disease. In the table, subjects who are homozygous for the mutation are denoted as m/m; subjects with only one mutated gene (heterozygous for the mutation) are denoted as A/m; and subjects with two normal alleles (homozygous for the absence of the mutation) are denoted as A/A. The unexposed category for the study is the A/A genotype. The neurologic condition is thought to be autosomal dominant with respect to the gene; therefore, one copy of the m allele should induce the development of the condition.

Using the odds ratio calculated Q8, what is the population attributable risk percent for the mutation?

a. 0%
b. 75%
c. **89%**
d. 99%
e. Cannot be calculated due to non-estimable odds ratio

To estimate this percentage, one must use Levin's formula with the odds ratio representing risk and the proportion of the mutation in controls representing the proportion of population with the exposure. In these data, the controls are representative of the population frequency of at least one m allele. The proportion having at least one m allele is 0.11 (48 divided by 433). When this proportion is placed in Levin's formula using the odds ratio of 75.4 as the risk, then the calculation is (0.11 × 74.4) / ((0.11 × 74.4) + 1). This gives the answer as 0.89, or 89%.

10. The data in the table below are from a case-control study of a genetic factor associated with neurologic disease. Cases are newly diagnosed persons with the rare neurologic condition, and population controls were used for comparison. Investigators have hypothesized that a single point mutation in a gene on the 10th chromosome is strongly related to the disease. In the table, subjects who are homozygous for the mutation are denoted as m/m; subjects with only one mutated gene (heterozygous for the mutation) are denoted as A/m; and subjects with two normal alleles (homozygous for the absence of

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the mutation) are denoted as A/A. The unexposed category for the study is the A/A genotype. The neurologic condition is thought to be autosomal dominant with respect to the gene; therefore, one copy of the m allele should induce the development of the condition.

Does this study confirm the hypothesis that the condition is caused by an autosomal dominant mutation? Why or why not?

a. Yes, the strength of association is very large
b. Yes, all homozygous persons for the mutation are cases
c. No, the odds of disease among heterozygotes is 0.46
d. No, the investigators have not done a prospective study
e. No, some of the cases are homozygous for the normal allele

If the mutation were autosomal dominant, then we would expect all persons with the m mutation to have the neurologic disease. Since this is not evidenced by the data, the hypothesis cannot be accepted.

11. The basis for the healthy worker effect is that:

a. Having a job makes people healthier and less susceptible to disease
b. Employment status is correlated with health status
c. Persons who work are less likely to be exposed to harmful agents
d. Persons who work have health insurance and receive better treatment
e. Studies of persons who work are confounded by socioeconomic status

The ability to obtain and keep a job depends upon some level of good health. Since persons who are in the workforce are more likely to have better health status, studies which compare worker populations to the general population typically find that workers have fewer adverse health outcomes than the general population. This leads to a self-selection bias in that persons who are selected into employment are more likely to be in good health

12. Epidemiologists were interested in investigating the relationship between exercise and development of coronary heart disease (CHD) among women. Women ages 45 to 55 years were interviewed to determine their exercise habits at entry into the study. They were then followed for 15 years to determine the incidence of CHD in the cohort. What proportion of women who developed CHD had exercised once per week?

Frequency of Exercise	Person-Years of Follow-up	Cases of CHD	Rate per 10,000 Person-Years	Rate Ratio
No exercise	32,843	23		Referent
Once per week	117,205,	40		
Twice per week	25,111	4		

The best answer is 60%. Sixty-seven cases of CHD occurred during the 15-year follow-up period. Forty of the cases (60%) developed in women who exercised once per week.

13. Epidemiologists were interested in investigating the relationship between exercise and development of coronary heart disease (CHD) among women. Women ages 45 to 55 years were interviewed to determine their exercise habits at entry into the study. They were then followed for 15 years to determine the incidence of CHD in the cohort. Complete the table by calculating the incidence rates per 10,000 person-years and the rate ratios.

Frequency of Exercise	Person-Years of Follow-up	Cases of CHD	Rate per 10,000 Person-Years	Rate Ratio
No exercise	32,843	23	7.00	Referent
Once per week	117,205	40	3.41	0.48
Twice per week	25,111	4	1.59	0.22

Rates per 10,000 person-years: 7.00, 3.41, 1.59 by increasing exercise frequency.
Rate Ratios: Referent, 0.49, 0.23 by increasing exercise frequency.
To calculate the rates per 10,000 person-years, divide the number of incident CHD cases by the total person-years exposed and multiply by 10,000 to standardize the rates. For example, among women who reported no exercise, 23 cases divided by 32,843 person-years gives a rate of 0.0007 events per person-year. After multiplying by 10,000, the rate equals 7.00 events per 10,000 person-years.
To estimate the rate ratio, one group must be designated the referent group. All estimated ratios are relative to this group's rate. In this study, the nonexposed group was comprised of women who reported no exercise at baseline. The rate ratio comparing the group exercising once per week to this referent category equals 3.41 divided by 7.00, or 0.49.

14. Epidemiologists were interested in investigating the relationship between exercise and development of coronary heart disease (CHD) among women. Women ages 45 to 55 years were interviewed to determine their exercise habits at entry into the study. They were then followed for 15 years to determine the incidence of CHD in the cohort. The investigators concluded that these data demonstrate a causal relationship between exercise and subsequent CHD. Which of the Hill criteria best applies to this data?

Frequency of Exercise	Person-Years of Follow-up	Cases of CHD	Rate per 10,000 Person-Years	Rate Ratio
No exercise	32,843	23		Referent
Once per week	117,205,	40		
Twice per week	25,111	4		

a. Biologic plausibility
b. Consistency
c. Specificity
d. Dose-response
e. Temporality

The rate ratio is a measure of relative risk for these three groups. It has a suggestive pattern that increasing exercise is correlated with less CHD.

15. Epidemiologists were interested in investigating the relationship between exercise and development of coronary heart disease (CHD) among women. Women ages 45 to 55 years were interviewed to determine their exercise habits at entry into the study. They were then followed for 15 years to determine the incidence of CHD in the cohort. Other epidemiologists disagreed that this was a causal finding. What error do they claim that the study investigators made when interpreting the study findings?

Frequency of Exercise	Person-Years of Follow-up	Cases of CHD	Rate per 10,000 Person-Years	Rate Ratio
No exercise	32,843	23		Referent
Once per week	117,205,	40		
Twice per week	25,111	4		

a. There is significant confounding by age
b. The data are not generalizable to the total population
c. Exposure is likely to be misclassified during the follow-up period
d. There is selection bias introduced by not randomizing the study participants to an exercise frequency
e. CHD is a heterogenous disease that manifests differently in each case

Though cohort studies have definite advantages for providing evidence for causal relationships between exposure and disease, one disadvantage of studies with long follow-up is the reliance on baseline exposure measures. Without further determination that women

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maintained their reported exercise frequency during the entire 15-year study, it is likely that there is information bias due to misclassification of exposure. (There are, however, statistical methods to take into consideration time-dependent variables.)

16. A cross-sectional study finds that persons younger than 70 years of age have a higher prevalence of pneumonia than those older than age 70. Which of the following is the best explanation for this observation?

- **a.** Persons younger than 70 have a higher incidence of pneumonia
- **b.** Persons younger than 70 have a higher case-fatality rate for pneumonia
- **c.** Persons younger than 70 are more likely to have complete follow-up in pneumonia studies
- **d. Incidence rates may be equal in both age categories; however, persons older than 70 have a shorter duration of pneumonia compared to those younger than 70**
- **e.** Persons younger than 70 are more likely to be exposed to pneumonia

Since the study is cross-sectional, all cases of disease are prevalent cases at the time of data collection. It is likely that the higher prevalence in the younger age group is due to either higher incidence or longer duration. In this instance, the second explanation is more compatible with the observation since pneumonia has a greater adverse effect on mortality among older persons.

17. Meat consumption may be a risk factor for colon cancer. This hypothesis was investigated by collecting data on the amount of red meat consumed in regions of the United States and the colon cancer rates in those areas. The data are shown below:

Region	Per Capita Red Meat Consumption	Annual Rate of Colon Cancer (per 100,000 persons)
Northeast	11.5 kg	320
Midwest	18.2 kg	410
Southeast	17.4 kg	380
West	13.6 kg	335

From these data, the researchers concluded that there is a significant dose-response association between red meat consumption and incident colon cancer. This observation may be incorrect because:

- **a.** No statistical test is presented to support the significance claim
- **b.** The data are not age-adjusted
- **c.** There may be confounding by preparation methods
- **d. The meat consumption habits of persons with colon cancer are not reported**
- **e.** The observation is correct

This cross-sectional study measures the average amount of red meat consumption in a population and attempts to correlate it with the incident rate for colon cancer. No data are presented that describe the individual red meat consumption levels for individuals with and without colon cancer. The study suffers from the problem of assigning group level measures to individuals. This error is known as the ecologic fallacy.

18. Meat consumption may be a risk factor for colon cancer. This hypothesis was investigated by collecting data on the amount of red meat consumed in regions of the United States and the colon cancer rates in those areas. The data are shown below:

Region	Per Capita Red Meat Consumption	Annual Rate of Colon Cancer (per 100,000 persons)
Northeast	11.5 kg	320
Midwest	18.2 kg	410
Southeast	17.4 kg	380
West	13.6 kg	335

Which designs can be used to evaluate this hypothesis?

- **a.** Case-control study
- **b.** Non-concurrent cohort study
- **c.** Concurrent cohort study
- **d. All of the above**
- **e.** None of the above

Each of the study designs can be adapted to test the association between red meat exposure and colon cancer using a variety of data collection strategies. The key issue is the determination of individual measures of red meat consumption as well as potential confounders. Pairing this data with valid ascertainment of incident colon cancer cases is essential to conducting an etiologic study.

19. Which of the following are characteristics of a disease that are important for the conduct of an effective screening program? More than one answer may be correct.

- **a. High prevalence of the disease**
- **b. The disease has a severe effect on health**
- **c.** Clear clinical symptoms associated with the disease

d. Treatment reduces the duration of the disease
e. There is a long latency period following biologic onset

20. Which factor can increase the positive predictive value (PPV) estimated for a screening program?
a. High sensitivity for the screening test used in the program
b. Selection of a screening population at high risk for the disease
c. Reduction of the negative predictive value (NPV) by removing false negative cases
d. Generalizability of the screening test
e. The disease is rare in the population

The PPV is the number of true positive cases of the disease among all persons identified by a screening test as having a disease. This value increases when there is a high level of risk for the disease in the population, thereby increasing the likelihood that a positively identified case truly has the disease. Less importantly, an increase in sensitivity may also increase the PPV by increasing the number of true positives.

21. When evaluating disease screening programs, what is a potential bias of the measure of their effectiveness when compared to symptom-based diagnostic approaches?
a. Confounding by age
b. Selection bias among persons who undergo screening tests
c. Recall bias by persons who undergo screening
d. Lead-time bias due to early detection of incurable disease
e. Ecologic fallacy

Sometimes screening programs can be effective at discovering more cases of a disease even though there is no adequate treatment program. This would serve to raise the incidence and prevalence of the disease; however, the effectiveness of this is reduced if mortality measures are not improved. This can occur when the disease has no effective treatment such that the screening program has no impact on the disease-specific mortality rate.

22. What is the epidemiologic transition?
a. Change from nonexposed to exposed status during a prospective study
b. Development of the study disease during follow-up
c. Reversal of the risk estimate after adjustment for a strong confounder
d. Reduction in proportion of deaths due to infectious diseases in the first part of the 20th century
e. Generalizability of study findings to the population

The epidemiologic transition is used to describe the period from 1860 through 1950 in which many scientific breakthroughs contributed to the substantial reduction of mortality caused by infectious diseases. Epidemiology was one of many sciences that contributed to the reduction in death and the increase in life expectancy due to the prevention of many infectious diseases. Ironically, it also served to increase the prevalence of chronic diseases such as cardiovascular disease and cancer due to the survival of many more persons to older ages.

23. For a cross-sectional study to be a valid test of a hypothesis, which of the following must be true?
a. Exposure is constant over time
b. Underlying risk of disease is constant over time
c. When a disease has no latency period and clinical symptoms manifest immediately after biologic onset
d. Individual exposure measures have the same distribution as group measures
e. The results of the study are externally valid (generalizable)

Cross-sectional studies typically collect information on exposure and disease at the same point in time. This approach is convenient for testing associations between exposure and disease, but it is inadequate for many types of etiologic research since temporality is a key assumption. When exposure is constant over time for individuals, or, better stated, it is fixed (e.g., blood type, specific gene, sex), then the cross-sectional study can be used to test an etiologic hypothesis since exposure is measured for a characteristic that has always been present for each individual in the study.

24. Which of the following measures is best suited to the evaluation of a screening program over time?
a. Incidence rate
b. Relative risk
c. Cause-specific mortality rate
d. Survival probability
e. Case-fatality rate

The cause-specific mortality rate is a measure of the rate of death among persons with a specific disease. An effective screening program aims to identify persons with disease at earlier stages such that treatment can be given for the disease. Over time, the best

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measure of a screening program is its impact on the cause-specific mortality rate as reductions in this rate can be attributed to the benefits of treatment at earlier stages of a disease.

25. After a hospital in a major city adds a high-risk pregnancy and neonatal intensive care unit (NICU), the rate of adverse childbirth outcomes doubles. Administrators are concerned that this indicates that the new unit is ineffectively run. Which of the following is a reason that this concern may be unfounded?

a. Incidence of congenital birth defects has been increasing
b. Childbirth procedures and personnel are still the same as before the addition
c. The type of population served by the new unit has changed
d. Many of the new mothers attending the unit are older at first birth
e. None of the above

In this instance, the addition of the new unit specializing in high-risk pregnancies most likely led to a selection bias. By expanding its services, the hospital increased the number of pregnancies and childbirths considered high risk, some of which could not be treated and resulted in adverse outcomes.

26. In a study of immigrants to a new country, the rate of cardiovascular disease (CVD) in migrants is equivalent to the rate of CVD in their home country. This rate is lower than the rate for first generation family members and for their country of adoption. Which of the following could explain this observation?

a. Migrants vary in age distribution and the rate of CVD needs to be age-adjusted to reflect this
b. Healthier persons tend to immigrate leading to selection bias
c. Migrants tend to maintain similar lifestyles to those of their country of origin
d. The disease is rare in the country of origin
e. Migration tends to occur after the biologic onset of CVD

Since the rate of CVD is similar between migrants and persons in their country of origin, this would suggest that there is a genetic component; however, this hypothesis is not adequate since first generation family members in the country of adoption have a different rate of CVD. Therefore, the most likely explanation is that migrants tend to retain cultural and other characteristics that are common to their country of origin such as diet, exercise habits, and other factors related to CVD.

27. A large cohort study of 1,000 adult pairs of twins was conducted. Seventy-two pairs of twins were concordant for the disease under investigation, and 94 pairs of twins were discordant for the disease. In the remaining twin pairs, neither adult had the disease. What is the concordance rate for this disease among all twin pairs with at least one affected member?

a. 7%
b. 17%
c. 25%
d. 43%
e. Cannot be determined

The concordance rate equals the number of twin pairs in which both members have the disease divided by the total number of pairs affected by the disease. This equals 72 pairs in which both twins have the disease divided by (72 + 94) pairs in which at least one member has the disease. This equals 0.43, or 43%.

28. A large cohort study of 1,000 adult pairs of twins was conducted. Seventy-two pairs of twins were concordant for the disease under investigation, while 94 pairs of twins were discordant for the disease. In the remaining twin pairs, neither adult had the disease. From this observation, what is the most likely interpretation?

a. Genetic factors are a major determinant of the disease
b. Environmental factors are a major determinant of the disease
c. Both types of factors are responsible for the disease
d. Neither type of factor is
e. Cannot be determined from these data

Since information is not given regarding zygosity, i.e., whether the twins are identical or fraternal, the high rate of concordance is not easily interpreted. Twins typically share both genetic and environmental factors, especially for early life exposures. In the absence of specific information concerning the disease and the types of twin pairs, it is not possible to determine the type of causal agent for this disease.

29. Within a large manufacturing company, the division responsible for the production of agricultural chemicals has an annual rate of lung cancer equal to 17.3 cases per 100,000 persons. The rate of lung cancer for the rest of the company not exposed to agricultural chemical production is 13.6 cases per 100,000 persons. What inference can be made concerning the association of agricultural chemical production and lung cancer within this company?

a. The association is real
b. The association is confounded by differences in age distribution
c. The association is not real since prevalence is not measured
d. The association may not be real due to confounding by other risk factors for lung cancer
e. The association is not real due to selection bias

The main risk factor for lung cancer is cigarette smoking. Without relevant information on the distribution of smoking by type of division within the company, the increase in lung cancer in the agricultural chemical production division may not be real.

30. For an etiologic factor to be judged to be causally related to a disease, which of the following must be true?

a. The etiologic factor is equally distributed throughout the population
b. The etiologic factor is found among all cases of the disease
c. Exposure to the etiologic factor must precede the onset of the disease
d. Persons exposed to the etiologic factor have a higher prevalence of disease
e. The results of an epidemiologic study of the factor must be externally valid

Of all criteria which are used to evaluate causality, temporality is the only essential factor for an etiologic relationship. Exposure to the etiologic factor must precede the onset of disease in all cases for the relationship to be causal. Epidemiology relies on the comparative distribution of disease in populations who are exposed or nonexposed to a suspected etiologic agent. Among these groups, only a proportion of persons develop the disease of interest. By making relative comparisons, epidemiologists study the risk of disease; however, causality requires a higher level of proof starting with temporality.

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CHAPTER 2

1. Answer: b
   The best answer is b. The term endemic is defined in the text as, "the habitual presence of a disease within a given geographical area." Therefore, the levels of an endemic disease may vary over time but the disease remains present in a population.
   Answer a is incorrect because this statement describes an epidemic. Answer c is incorrect since this statement describes a pandemic disease when the disease levels are greater than expected, and is not a necessary condition for an endemic disease. Answer d may be a characteristic of specific endemic diseases; however, it is not true for all endemic diseases. Finally, answer e describes a zoonotic disease.
2. Answer: a
   The best answer is a. The attack rate is defined as the number of people at risk in whom a certain illness develops divided by the total number of people at risk. The attack rate for those who ate both tuna and egg salad is as follows:

$$= \frac{\text{People who developed sore throat who ate both tuna and egg salad}}{\text{People who aate both tuna and egg salad}}$$

$$= \frac{60}{75}$$

   Answer b is not correct as 70/200 is the proportion of persons who got sick from eating tuna only. Answer c is not correct as this ratio counts the sick persons who ate both foods twice in the denominator (75 people ate both tuna and egg salad + 60 people ate both foods and became sick = 135). Answer d is not correct as this proportion combines the persons who ate both foods and those who ate tuna only in the denominator (75 people ate both tuna and egg salad + 200 ate tuna only = 275). Finally, answer e is not correct as answer a expresses the correct attack rate.
3. Answer: b
   The best answer is b. In order to determine which food item is most likely to be infective, it is helpful to compute cross-tabulations. A cross-table analysis of egg salad and tuna would provide the following results:

	Sick	Well	Total	Attack rate	Sick	Well	Total	Attack rate
Ate egg salad	60	15	75	80%	75	25	100	75%
Did not eat egg salad	70	130	200	35%	15	35	50	30%

   Attack rate for those who ate both egg and tuna salad:

$$= \frac{\text{Those sick who ate both egg and tuna salad}}{\text{Those who ate both egg and tuna salad}}$$

$$= \frac{60}{75}$$

$$= 0.80, \text{or } 80\%$$

   Attack rate for those who ate egg salad only:

$$= \frac{\text{Those sick who ate egg salad only}}{\text{Those who ate egg salad only}}$$

$$= \frac{75}{100}$$

$$= 0.75, \text{ or } 75\%$$

   Attack rate for those who ate tuna salad only:

$$= \frac{\text{Those sick who ate tuna salad only}}{\text{Those who ate tuna salad only}}$$

$$= \frac{70}{130}$$

$$= 0.35, \text{ or } 35\%$$

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Attack rate for those who ate neither egg nor tuna salad:

$$= \frac{\text{Those sick who ate neither egg nor tuna salad}}{\text{Those who ate neither egg nor tuna salad}}$$

$$= \frac{15}{35}$$

$$= 0.30, \text{ or } 30\%$$

From the table it is observed that those who ate egg salad had higher attack rates than those who did not eat egg salad (75% vs. 30%). Thus the egg salad is implicated as the most infective agent. Answers a and d are not correct since the attack rate in persons who ate tuna only is similar to that of the persons who ate neither food (35% vs. 30%). Answer c is not correct due to the high attack rate in those who ate egg salad only. Finally answer e is incorrect since there is sufficient data to calculate the attack rates.

4. Answer: d
   The best answer is d. An epidemic curve is the distribution of the times of onset of a disease. Plotting an epidemic curve helps to determine the type of outbreak that has occurred, for example, a single exposure outbreak may be unimodal with a long right tail whereas a multiple exposure outbreak may be bimodal (answer a). Plotting the epidemic curve also allows for the estimation of the median incubation period (answer c).
   Answer b is incorrect since an epidemic curve is not useful for showing whether herd immunity occurred since those who do not develop the disease, i.e., the immune, are not represented in the epidemic curve.
5. Answer: c
   The best answer is c. There are three characteristic features of a single-exposure common vehicle outbreak which include: (1) it is explosive (since all cases are exposed at the same point in time, there is a sudden and rapid increase in the number of cases in a population); (2) the cases are limited to people who share the common exposure; and (3) cases rarely occur in persons who acquire the disease from a primary case.
   Answer b is incorrect since increasing severity with increasing age is a common characteristic of many infectious disease outbreaks and not just single-exposure common- vehicle. Answer c is incorrect because there are rarely secondary cases in a single exposure outbreak. Answer d is not correct since cases only include those who are exposed to the infectious agent. Finally, answer e is incorrect since only one statement is applicable.
6. Answer: c
   Although Ebola virus disease, MERS-CoV, and measles are serious diseases (answers a, b, and d), they are generally localized and sporadic and are not affecting significant portions of the world's population; only H1N1 flu virus (answer c) is truly pandemic.

CHAPTER 3

1. Answer: e
   The best answer is e. The inference is incorrect because a comparison of risk involves comparing measures of disease incidence. The example describes the prevalence of migraine headache in men and women of the same age group. Prevalence represents all cases of a disease in a population at the time of examination; therefore, it is influenced by the duration of time that individuals have a disease. Incidence is the total number of cases of a disease that develop during a specified time interval divided by the total number of persons at risk for the disease for the same time period. Since incidence measures the transition from nondiseased to diseased status, it is considered a measure of risk.
   Statement a is wrong as the inference is incorrect. Statement b is wrong because two prevalence ratios are presented; however, they do not describe risk. Statement c is wrong because the comparison is restricted to a single age group. Statement d is wrong because data are given to compare men and women; however, additional information is needed to describe risk.
2. Answer:
   To calculate the number of new cases in the population:

$$= \frac{\text{Number of new cases in a population over a given time period}}{\text{Number of people at risk during that time period} * \text{Total population}}$$

$$= \frac{5}{100{,}000 * 2{,}000{,}000}$$

$$= 100 \text{ new cases in 2003}$$

To get the percent of newly diagnosed cases:

$$= \frac{\text{New cases in 2003}}{\text{Total cases in 2003}}$$

$$= \frac{100}{1{,}000}$$

$$= 0.10, \textit{or}\ 10\%$$

3. Answer: d
   The best answer is c. Active surveillance denotes a system in which assigned staff make periodic visits to health care facilities to collect information for new cases of disease or other health outcomes. One advantage of active surveillance is the reduction of reporting burden for health care providers when they detect a new case of disease as this information will be collected by the surveillance staff who initiate contact with the facility.
   Statement a is not true since active surveillance requires designation of staff members specifically for disease reporting and staff size will increase with the number of diseases or the size of the population under surveillance. Statement b is incorrect since active surveillance also imposes a financial burden for hiring, training, and maintaining teams of persons to do these functions. Statement d is not true as surveillance reports depend on a consistent case definition to identify disease events. Statement e is wrong since active surveillance systems require intense investments of time and resources.
4. Answer: c
   The best answer is c. Since women who have had hysterectomies are not at risk for developing uterine cancer, the removal of these women from the denominator will cause the rates to increase, but the same number of age-specific incident cases will remain in the numerator for each rate calculation.
   Statement a is incorrect since the rates will change with the removal of women with hysterectomies from the denominator. Statement b is wrong since the rates would only decrease with a reduction in the number of uterine cancer cases, the numerator, or an increase in the number of women at risk, the denominator, which does not happen in this example. Statement d in incorrect because the premise of the question is that each age group contains women who have had hysterectomies; therefore, the denominator will decrease and thus rates increase in all age groups. Statement e is wrong because the removal of women with hysterectomies will affect the denominator only as no cases will occur in women who have had hysterectomies. Therefore it can be determined that the rate will decrease.
5. Answer: d
   Statement d is the best answer. The interpretation is incorrect because the data presented only describe the percentages of persons diagnosed with hypertension by age. These percentages reflect age-specific prevalence rates of hypertension in the population and do not contain information on incidence which is necessary to describe risk. Incidence is calculated as the number of new cases of disease in a population in a specific time period divided by the number of persons at risk of disease in the population during the specific time period. This example lacks a specified time period. Thus only prevalence data are presented. Statement b is incorrect because rates were presented, but only in terms of prevalence, so no inference on risk can be made. Statement c is wrong because incidence rates do describe risk, but they are not given in this answer. Statement d is the best answer because prevalence is not a measure of risk. Statement e is incorrect because no comparisons are being made between populations. This is a requirement for age adjustment as this technique adjusts for differences in the age structures between two populations to compare disease rates between these populations.
6. Answer: b.
   To calculate incidence:

$$= \frac{\text{Number of new cases in a population over a given time period}}{\text{Number of people at risk during that time period}}$$

$$= \frac{\text{26 new cases of TB}}{\text{Population of 183,000 during the 6-month period}}$$

$$= 0.00014, \text{or } 14 \text{ per } 100{,}000$$

7. Answer: c.
   To calculate prevalence:

$$= \frac{\text{Number of cases in a population}}{\text{Population at the time of enumeration}}$$

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$$= \frac{264 \text{ cases of TB}}{\text{Population of 183,000 during the 6-month period}}$$

$$= 0.00144{,}144 \text{ per } 100{,}000$$

8. Answer: c
   Answer a is wrong because we do not know whether duration of X and Y are due to cure or death. Answer b is wrong, per the following formula. Incidence rates are the same for X and Y, and thus answer d is incorrect. Answer e is incorrect, given that duration is given in the question and it is higher for disease X than for disease Y. Using the formula, "prevalence = incidence[Symbol] duration," a higher prevalence is expected for disease X because 15 [Symbol] 5 = 75 per 100,000, whereas prevalence for disease Y is only 5 years [Symbol] 5 per 100,000 person-years = 25/100,000. Note that, to use this formula, it is assumed that incidence has been stable over time and that the prevalence of the disease is low (as it is). Thus the correct answer is c.
9. Answer: d
   Answer a is incorrect because to calculate proportional mortality it would be necessary to know the total number of deaths, which is not given. Answer b is incorrect because dividing mortality by incidence approximately estimates case-fatality, which is lower for disease B. Answer c is incorrect because the lower incidence and higher case fatality associated with disease A result in the accumulation of fewer prevalent cases than those for disease B. Answer e is incorrect because to calculate YPLL it is necessary to have information on age at death. The correct answer is d because disease B has a higher incidence and a lower case-fatality than disease A.
10. Answer: d
    Answer a is incorrect because it gives only the numerator of the rate. Answer b is incorrect because prevalence, the numerator of which is based on the number of total existing cases, is not provided. Answer c is incorrect because the total number of deaths from Chikungunya infection is not given. Answer e is not correct because cumulative survival is the reciprocal of the cumulative incidence rate and answer e shows only the cumulative incidence rate. The right answer is d, which is obtained by dividing the total number of newly infected people by the total population.

CHAPTER 4

1. Answer:
   The cause-specific mortality rate is calculated as:

$$= \frac{\text{The number of deaths from a specific cause}}{\text{The number of persons in the population}}$$

$$= \frac{30{,}000 \text{ deaths}}{6{,}000{,}000 \text{ people}}$$

$$= 0.005, \text{ or } 5 \text{ deaths per } 1{,}000 \text{ people}$$

2. Answer:
   The case-fatality rate (CFR) is calculated as:

$$= \frac{\text{The number of individuals dying during a specified period of time after disease onset}}{\text{The number of individuals with the specified disease}}$$

$$= \frac{30{,}000 \text{ deaths}}{100{,}000 \text{ infected persons}}$$

$$= 0.30, \textit{ or } 30\%$$

3. Answer: e
   The best answer is e. Mortality data are sometimes used to compare two or more populations. Sometimes populations may differ with regard to characteristics that may affect mortality. The most important factor that affects mortality is age. In order to compare death rates in two populations adjusting for the effect of age, several techniques have been developed. Therefore, the purpose of age-adjusted death rates is to eliminate the effects that differential age distributions between populations have when mortality rates are compared. Answer a is incorrect because this implies that it corrects for individual reports of age not the age structure of the population. Answer b is not correct because the actual number of deaths have already been observed whereas age adjustment can sometimes be used to estimate the expected number of deaths in a population if it shared the same age structure as a referent population. Answer c is not correct because age adjustment cannot account for missing data. Finally d is not correct because age-adjusted death rates may be used to compare deaths in persons of the same age group; however, this comparison may be biased for other

reasons and may not be corrected by age adjustment alone.

4. Answer: b
   The best answer is b. The inference is incorrect because mortality data are presented for the two cities. Prevalence of a disease is typically a morbidity measure and does not represent the same concept as mortality. Therefore, the inference is incorrect because of the failure to distinguish between mortality and prevalence. The mortality rate is higher in city B, but it is incorrect to state that the prevalence is also higher in city B since the prevalence of the disease could be the same in the two cities with city B having a higher case-fatality rate.
   Answer a is not correct since the infernce is wrong. Answer c is incorrect since adjustment for age distribution does not need to be made as comparisons are within the same age category. Answer d is incorrect since prevalence is not discussed in this example. Finally, answer e is incorrect since mortality rates are presented.
5. Answer: b
   The best answer is b. Prevalence equals incidence times duration for a disease. If the prevalence rate shows no sex difference, but the incidence rate is five times greater in women than in men, then the duration of disease must be shorter in women. The duration of disease can be shorter for women either because the recovery rate is higher in women or the case-fatality rate is greater in women. Since there is no option discussing the recovery rate, then the correct statement is that the case-fatality rate is greater in women.
   Answer a is incorrect since no data are presented for all-cause mortality rates. Answer c is incorrect since the case-fatality rate for this disease could be higher in women and this would be opposite of the correct answer (above). Answer d is incorrect since the case-fatality rate or recovery must be greater in men than women for duration of disease to be shorter in men, and this is not consistent with the information given. Answer e is incorrect since the question presents no data concerning risk factors for this disease in women.
6. Answer: a
7. Answer: 2.5 or 250
8. Answer: d
   The best answer is d. The data shown are for proportionate mortality defined as the number of deaths from a particular disease divided by the total number of deaths. Proportionate mortality is a proportion. It is not a rate so it cannot be used to make inferences about the risk of death in populations. In order to compare the risk of death from a specific cause in two groups, the cause-specific mortality rate must be used. This rate is a measure of risk in the populations. Only rates allow for inference about risk.
   Answer a is not correct since the conclusion is mistaken. Answer b is incorrect because it assumes proportionate mortality is a rate. It is a ratio that is expressed as a percentage. Answer c is incorrect, as the two industries are compared to each other. Finally, answer e is not correct since d is valid.
9. Answer: c
10. Answer: d
    The best answer is d. Standardized mortality ratios (SMRs) are useful for addressing whether a population, composed of workers in a certain industry, has higher mortality than would be expected if the population had the same mortality rate as those who do not work in the industry, i.e., in the general population. SMRs are computed by dividing the observed number of deaths by the expected number of deaths. This is typically referred to as an indirect method of age adjustment. When the ratio is greater than 1 (or 100 if multiplied by this amount to remove the decimal), then the inference is that the occupational cohort has a higher mortality rate than would be expected for a similar group of men of all ages who are representative of a wide range of occupations, not just carpentry.
    Answer a is incorrect since the SMR is a ratio and does not indicate the absolute number of deaths from lung cancer in either group. Answer b is not correct since the SMR indicates only the ratio between observed and expected lung cancer deaths. Neither the number of lung cancer deaths nor the number of total deaths in bricklayers is not provided, making the estimation of proportionate mortality impossible using this table. Answer c is incorrect because the lung cancer mortality rate cannot be inferred from the SMR. The ratio shown in the table expresses the proportion of observed to expected deaths in each period. Finally, answer e is incorrect since standardized mortality ratios are not directly comparable to proportionate mortality rates. Proportionate mortality is defined as the

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number of deaths from a particular disease divided by the total number of deaths. This requires knowing the absolute number of observed deaths due to lung cancer and the total number of all deaths in the group.

11. Answer:
In order to calculate the age-adjusted death rate for disease Z in communities X and Y by the direct method, the total of both communities can be used as the standard population. This results in the following table:

Expected number of deaths in Community X:

= Expected number of deaths in young people in Community X + expected number of deaths in old people in Community X

Expected number of deaths for young people in Community X:

Age	No. of People	No. of Deaths from Disease Z	*Death Rate per 1,000*	*Expected No. of Deaths*	No. of People	No. of Deaths from Disease Z	Death Rate per 1,000	Expected No. of Deaths
Young	8,000	69	8.63	112.13	5,000	48	9.60	124.80
Old	11,000	115	10.45	146.36	3,000	60	20.00	280.00
Totals	19,000			258.49	8,000			404.80

= Death rate for young people in Community X * the combined population of young people

Death rate for young people in community X:

$$= \frac{69}{8,000}$$

$$= 0.00863$$

The combined population of young people:

$$= 8,000 + 5,000$$

$$= 13,000$$

$$= 0.00863 * 13,000$$

$$= 112.13$$

Expected number of deaths for old people in Community X:

= Death rate for old people in Community X * the combined population of young people

Death rate for old people in Community X:

$$= \frac{115}{11,000}$$

$$= 0.01045$$

The combined population of young people:

$$= 11,000 + 3,000$$

$$= 14,000$$

$$= 0.01045*14,000$$

$$= 146.36$$

= Expected number of deaths in young people in Community X + expected number of deaths in old people in Community X

$$= 112.13 + 146.36$$

$$= 258.49$$

Expected number of deaths in Community Y: (Not required, but calculations included for those interested.)

= Expected number of deaths in young people in Community Y = expected number of deaths in old people in Community Y

Expected number of deaths for young people in Community Y:

= Death rate for young people in Y * the combined population of young people

Death rate for young people in Community Y:

$$= \frac{48}{5,000}$$

$$= 0.0096$$

The combined population of young people:

$$= 8{,}000 + 5{,}000$$

$$= 13{,}000$$

$$= 0.0096 * 13{,}000$$

$$= 124.80$$

Expected number of deaths for old people in Community Y:

= Death rate for old people in Community Y * the combined population of young people

Death rate for old people in Community Y:

$$= \frac{60}{3{,}000}$$

$$= 0.02$$

The combined population of young people:

$$= 11{,}000 + 3{,}000$$

$$= 14{,}000$$

$$= 0.02 * 14{,}000$$

$$= 280.00$$

= Expected number of deaths in young people in Community Y + expected number of deaths in old people in community Y

$$= 124.80 + 280.00$$

$$= 404.80$$

The age-adjusted rate of disease Z in Community X:

$$= \frac{\text{Number of total expected deaths}}{\text{Total combined population}}$$

$$= \frac{112.13 + 146.36}{27{,}000}$$

$$= 0.0096, \text{ or } 9.6 \text{ per } 1{,}000$$

The age-adjusted rate of disease Z in Community Y: (Not required, but calculations included for those interested.)

$$= \frac{\text{Number of total expected deaths}}{\text{Total combined population}}$$

$$= \frac{124.80 + 280.00}{27{,}000}$$

$$= 0.015, \text{ or } 15.0 \text{ per } 1{,}000$$

12. Answer: e
The best answer is e. Proportionate mortality is defined as the number of deaths from a particular disease divided by the total number of deaths. The total number of deaths from disease Z in Community Y is 108. But data are not given as to the total number of deaths from all causes (the denominator for proportionate mortality); therefore, the proportionate mortality for disease Z in Community Y cannot be calculated. This means that answers a through d are incorrect.
13. Answer: d
Answer a is not true because both the crude and age-adjusted mortality of Community Z are the same (9.6/1000) and lower, not higher, than the crude mortality rate of Community Y. (Note that age adjustment did not change the mortality rate in Community X, which means that age was not a confounder.) Answer b is not true either because allocation of funds should be based on crude (real!), rather than adjusted rates. Percentage of deaths is not used as weights in direct age-adjustment, which makes answer c untrue. The difference in adjusted mortality rates between the communities may be due to causes other than age differences (e.g., a difference in the incidence of a highly lethal disease). Thus answer e is not true either. The true statement is d: for direct adjustment, the weight for each age group represents the standard population for that group. A standard population is therefore a set of weights, and the adjusted rate is a weighted average rate.
14. Answer: a
Answer d is incorrect because standardization is done both to compare standardized with crude rates, and between-population rates. Answer e is incorrect because proportionate mortality rate is calculated as number of deaths from a specific cause as a percentage of the total number of deaths and thus has a denominator different from that of the mortality rate. Because mortality rates are higher in those aged 65 years and older and because, in addition, the standard population has a lower proportion of those

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aged 65 years or older, there would be a decrease in the US standardized mortality rate vis-à-vis its crude rate mortality rate. Thus answer a is correct and answers b and c are incorrect.

15. Answer: b
Answer c is incorrect because identical case fatality for myocardial infarction does not have to be assumed to examine mortality. Answer d is incorrect because a mortality pattern consistent with a protective effect of fish oil can only be inferred from a comparison of risks of death between the fish processing plant and the brewery. Answer e is incorrect because prevalence rates do not have to be known when examining mortality risks. Answer b is correct (and thus answer a is incorrect) because risk of death (mortality) and proportional mortality are different indices of mortality. It is not correct to infer risk of death from proportionate mortality.

CHAPTER 5

1. Answer:
In order to compute sensitivity,* it is helpful to complete a 2 × 2 table as below:

	BIOPSY-PROVEN ADENOCARCINOMA		
Physical Examination	**Yes**	**No**	**Totals**
Positive	1,800	800	2,600
Negative	700	4,200	4,900
Totals	2,500	5,000	7,500

Sensitivity of the physical examination:

$$= \frac{\text{Persons with the disease correctly identified by the test}}{\text{Persons with the disease}}$$

$$= \frac{1{,}800}{2{,}500}$$

$$= 0.720, \text{ or } 72.0\%$$

*Note: Sensitivity can also be calculated as follows:

$$= \frac{\text{True positives (TP)}}{\text{True positives (TP)} + \text{false negatives (FN)}}$$

$$= \frac{1{,}800}{1{,}800 + 700}$$

$$= 0.720, \text{ or } 72.0\%$$

2. Answer:
Specificity of the physical examination: *

$$= \frac{\text{Persons without the disease correctly identified by the test}}{\text{Persons without the disease}}$$

$$= \frac{4{,}200}{5{,}000}$$

$$= 0.840, \text{ or } 84.0\%$$

*Note: Specificity can also be calculated as follows:

$$= \frac{\text{True negatives (TN)}}{\text{True negatives (TN)} + \text{false positives (FP)}}$$

$$= \frac{4{,}200}{4{,}200 + 800}$$

$$= 0.840, \text{ or } 84.0\%$$

3. Answer:
Positive predictive value (PPV) of the physical examination: *

$$= \frac{\text{Persons with the disease correctly identified by the test}}{\text{Persons the test identifies as having the disease}}$$

$$= \frac{1{,}800}{2{,}600}$$

$$= 0.692, \text{ or } 69.2\%$$

*Note: PPV can also be calculated as follows:

$$= \frac{\text{True positives (TP)}}{\text{True positives (TP)} + \text{false positives (FP)}}$$

$$= \frac{1{,}800}{1{,}800 + 800}$$

$$= 0.692, \text{ or } 69.2\%$$

4. Answer: d
The best answer is d. By definition the proportion of false-positive results among those who test positive is 1 minus the positive predictive value. If this number is lower in population A, then population A has a higher positive predictive value. As the disease prevalence increases, the positive predictive value

increases. Population A has a higher positive predictive value; therefore, the disease must be more prevalent in population A.

Answer a is not correct since adequate information is provided to infer the explanation for the finding. Answers b and e are incorrect since specificity is a characteristic of a test and does not change when the test is applied to different populations with varying disease prevalence. Answer c is incorrect since the prevalence of disease must be higher in population A as the positive predictive value is higher in population A (refer to text).

5. Answer: d

Answer d is the best answer based upon the following calculations.

Sensitivity of the physical examination:

$$= \frac{\text{Persons with the disease correctly identified by the test}}{\text{Persons with the disease}}$$

$$= \frac{240}{300}$$

$$= 0.800, \text{ or } 80\%$$

Sensitivity of the audiometric test:

$$= \frac{\text{Persons with the disease correctly identified by the test}}{\text{Persons with the disease}}$$

$$= \frac{270}{300}$$

$$= 0.900, \text{ or } 90.0\%$$

Specificity of the physical examination:

$$= \frac{\text{Persons without the disease correctly identified by the test}}{\text{Persons without the disease}}$$

$$= \frac{160}{200}$$

$$= 0.800, \text{ or } 80.0\%$$

Specificity of the audiometric test:

$$= \frac{\text{Persons without the disease correctly identified by the test}}{\text{Persons without the disease}}$$

$$= \frac{140}{200}$$

$$= 0.700, \text{ or } 70\%$$

6. Answer: b

The best answer is b. The sensitivity of the test is higher for Dr. Childs than for Dr. Kidd. Dr. Childs will correctly identify a greater proportion of diseased people by the new test. This can also be interpreted as Dr. Kidd correctly identifying fewer children who actually have streptococcal infection with the standard culture test.

Answer a is incorrect because Dr. Kidd's test has a lower sensitivity. Answer c is incorrect as the proportion of nondiseased people who are correctly identified as negative by the test will be the same for the two doctors since both tests have a specificity of 96%. Answer d is incorrect since sensitivity and specificity are characteristics of the test itself and do not depend upon disease prevalence.

7. Answer:

In a hypothetical population of 10,000 people:

Hemoccult Test	Yes	No	Totals
Positive	84	2.470	2,554
Negative	36	7,410	7,446
Totals	120	9,880	10,000

The following calculations were used to create the number above:

Total number of diseased people in the population:

$$= \text{Prevalence} * \text{total population}$$

$$= 12/1{,}000 * 10{,}000$$

$$= 120$$

Total number of nondiseased people in the population:

$$= \text{Total population} - \text{diseased people in the population}$$

$$= 10{,}000 - 120$$

$$= 9{,}880$$

Total number of people identified correctly by the test as having the disease (TP):

$$= \text{Sensitivity (TP/TP+FN)} * \text{total diseased people in the population (TP+FN)}$$

$$= 0.70 * 120$$

$$= 84$$

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Total number of people identified incorrectly by the test as not having the disease (FN):

$$= \text{Total diseased people in the population (TP+FN)} - \text{those with the disease correctly identified by the test (TP)}$$

$$= 120 - 84$$

$$= 36$$

Total number of people identified correctly by the test as not having the disease (TN):

$$= \text{Specificity (TN/TN+FP)} * \text{total nondiseased people in the population (TN+FP)}$$

$$= 0.75 * 9{,}880$$

$$= 7{,}410$$

Total number of people identified incorrectly by the test as having the disease (FP):

$$= \text{Total diseased people in the population (TN+FP)} - \text{those with the disease correctly identified by the test (FP)}$$

$$= 9{,}880 - 7{,}410$$

$$= 2{,}470$$

Positive predictive value (PPV) of the hemoccult test:*

$$= \frac{\text{Persons with the disease correctly identified by the test}}{\text{Persons the test identifies as having the disease}}$$

$$= \frac{84}{2{,}554}$$

$$= 0.033, \text{ or } 3.3\%$$

*Note: PPV can also be calculated as follows:

$$= \frac{\text{True positives (TP)}}{\text{True positives (TP)} = \text{false positives (FP)}}$$

$$= \frac{84}{84 + 2{,}470}$$

$$= 0.033, \text{ or } 3.3\%$$

8. Answer: b
The best answer is b. The method of testing described in this example is called sequential testing. By applying sequential tests, there is a loss of net sensitivity and a gain in net specificity.
Answer a is incorrect since both test characteristics are not increased in a sequential testing approach. Answer c is incorrect since the test characteristics undergo a trade-off when multiple tests are performed. This means that any gain in one must be balanced by a loss for the other. Answer d is incorrect since this describes the result of simultaneous testing. Finally, answer e is incorrect because adequate information exists to evaluate the effect on the tests.

9. Answer
Overall percent agreement:

$$= \frac{\text{Total number of concordant normal and abnormal test results}}{\text{Total individuals tested}}$$

$$= \frac{30 + 40}{100}$$

$$= 0.700, \text{ or } 70.0\%$$

10. Answer
Overall percent agreement removing the x-rays both physicians classified as normal:

$$= \frac{\text{Total number of concordant abnormal test results}}{\text{Total test results where at least one physician concluded the test was abnormal}}$$

$$= \frac{40}{70}$$

$$= 0.571, \text{ or } 57.1\%$$

11. Answer:
Kappa is:

$$= \frac{(\text{Percent agreement observed}) - \left(\begin{array}{c}\text{Percent agreement expected} \\ \text{by chance alone}\end{array}\right)}{100\% - \left(\begin{array}{c}\text{Percent agreement expected} \\ \text{by chance alone}\end{array}\right)}$$

Percent agreement observed:

$$= \frac{\text{Total number of concordant normal and abnormal test results}}{\text{Total individuals tested}}$$

$$= \frac{30 + 40}{100}$$

$$= 0.700, \text{ or } 70.0\%$$

Percent agreement expected by chance alone:

$$= \frac{\text{(Expected abnormal results} = \text{expected normal results}}{\text{Total individuals tested}}$$

= (Overall abnormal rate of physician 2 * total abnormal results identified by physician 1) + (Overall normal rate of physician 2* total normal results identified by physician 1)

Total individuals tested

$$= \frac{= \left[\left(\frac{50}{100}\right) * 60 = \left[\frac{50}{100}\right) * 40\right]}{100}$$

$$= 0.500, \text{ or } 50.0\%$$

$$= \frac{\text{(Percent agreement observed)} -}{\text{(Percent agreement expected by chance alone)}}{100\% - \left(\text{Percent agreement expected by chance alone}\right)}$$

$$= \frac{70.0\% - 50.0\%}{100\% - 50.0\%}$$

$$= 0.40, \text{ or } 40.0\%$$

12. Answer: b
The best answer is b. A kappa of 40% is classified as intermediate to good.
Answer a is incorrect since a kappa above 75% would indicate excellent agreement and answer c is incorrect since a kappa below 40% would indicate poor agreement.

CHAPTER 6

1. Answer:
The probability of surviving 3 years:

= The probability of surviving 1 year* the probability of surviving 2 years* the probability of surviving 3 years

The probability of surviving 1 year:

$$= \frac{\text{The number of patients alive at the end of the first year}}{\text{The number of patients enrolled}}$$

$$= \frac{152}{180}$$

$$= 0.844$$

The probability of surviving 2 years:

$$= \frac{\text{The number of patients alive at the end of the second year*}}{\text{The number of patients enrolled for whom there is data for more than 1 year}}$$

$$= \frac{87}{152 - 37}$$

$$= 0.757$$

*Note: The total patients on whom there is data for more than 1 year equals the patents alive at the end of the first year minus those who were only followed for 1 year (152-37).
The probability of surviving 3 years:

$$= \frac{\text{The number of patients alive at the end of the second year}}{\text{The number of patients enrolled for whom there is only data for more than 2 years*}}$$

$$= \frac{48}{87 - 31}$$

$$= 0.857$$

*Note: The total patients on whom there is data for more than 2 years equals the patients alive at the end of the second year minus those who were only followed for 2 years (87-31)

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= The probability of surviving 1 year * the probability of surviving 2 years * the probability of surviving 3 years

= 0.844* 0.757*0.857

= 0.547, or 54.7%

2. Answer: c
   The best answer is c. In using life tables, an important assumption is that there has been no change in treatment or in survivorship over the time period. Therefore, we can assume that treatment or in survivorship over the time period. Therefore, we can assume that treatment in one calendar year is the same as in another calendar year.
   Answer a is incorrect because improvement in treatment during the study period violates the fundamental assumption for computing survival probabilities using life tables. Answer b is incorrect because if improvement in the quality of record keeping over the study period occurred then the data from year to year is not comparable. Answer d is incorrect since survival analysis does not depend upon an equal amount of men and women being enrolled unless it is associated with mortality and has changed over time. Finally, answer e is incorrect since c is valid.
3. Answer: c
   The best answer is c. The case-fatality rate (CFR) is defined as the number of people who die of a disease divided by the number of people who have the disease. Although it is called a rate, the CFR does not explicitly include a statement of time. The time period covered by the CFR for a short term acute disease is typically the period shortly after diagnosis when death is lively to occur. Therefore, the CFR is a good index of severity for short-term acute diseases.
   Answer a is not correct because the cause-specific mortality rate estimates the number of death from a disease in the entire population at risk. This usually includes a substantial percentage of nondiseased persons in the denominator and thus would not be a good index for the severity of the disease in those afflicted. Answer b is not correct because 5-year survival is typically used for chronic diseases such as cancer. For an acute disease, the CFR is preferred. Answer d is incorrect because the SMR relies on an external population to provide expected numbers of deaths in order to compare this total with observed deaths. Usually a longer time period is necessary for an adequate number of deaths to occur in the population so it is not a reliable index when studying the short-term severity of a disease. Finally, answer e is incorrect since answer c satisfies the question.
4. Answer: b
   The best answer is b. If a disease is detected earlier but this has no effect on the natural history of disease, then the 5-year survival from that disease will increase. Since the patient will die at the same time as they would have died prior to early detection, then early detection means that the individual will be living longer with a diagnosis of the disease. This will increase the 5-year survival estimate.
   Answer a is incorrect because early detection of the disease will lead to an increase of cases that will increase the period prevalence over the 10-year period. Answers c and d are incorrect as the age-adjusted mortality rate will remain constant since early detection of the disease has no impact on the natural history of disease. Therefore, individuals will die from this disease at the same rate they did previously. Answer e is incorrect as incidence will only decrease if the prevalence or duration of the disease decreases and neither of these are applicable to this example.
5. Answer: c
   The best answer is c. Relative survival is defined as the ratio of the observed survival in a population to the expected survival in that population if they did not have the disease. In younger populations, observed and relative survival are similar due to the fact that the expected survival is close to 100%. This is because the expected mortality rate in younger populations is very low making the observed rate close to the relative rate.
   Answer a is incorrect as the term "relative" in this example does not have anything to do with family relations. Answer b is incorrect since elderly populations have lower expected survival, i.e., the overall mortality rate is high. Therefore, relative survival will differ from observed survival. Answer d is incorrect since relative survival differs from observed survival by the estimate of expected survival which can vary and is not constant. Expected survival depends upon age and the disease of interest. Answer e is not correct since c is correct.

6. Answer:
   The final four columns of the table are calculated as indicated below:
   The probability of dying in the third year, given that a person survived the second year, is found in column (6) of the table in the third row. This equals 0.982, or 98.2%.
7. Answer:
   The cumulative probability that a person enrolled in the study will survive to the end of the third year is found in column (8) in the third row. This equals 0.006, or 0.6%.
8. Answer: c
   The best answer is c. The second assumption made in the calculation of survival probabilities is that the survival experience of the people who are lost to follow-up is the same as the experience of those who remain in the study. In order to check this assumption one typically compares the baseline characteristics of those who remained in the study to those who were lost to follow-up.
   Answer a is incorrect because there was no randomization of exposure. All patients were given the new treatment. Answer b is incorrect since a check of prognostic change would require stratification of the data by time period in order to compare the early data to the later data. Answer d is incorrect since the 42 persons were lost to follow-up, so the outcomes for these individuals cannot be determined. Finally, answer e is incorrect as there are no exposed and unexposed groups in this analysis.

(5) Effective Number Exposed to Risk of Dying during Interval: Col(2)-0.5[Col(4)]	(6) Proportion Who Died during Interval: $\frac{\text{Col}(3)}{\text{Col}(5)}$	(7) Proportion Who Did Not Die during Interval: 1-Col(6)	(8) Cumulative Proportion Who Survived from Enrollment to End of Interval: Cumulative Survival
248-0.5* 27=234.5	96/234.5=0.4094	1-0.4094=0.5906	0.5906
125-0.5* 13=118.5	55/118.5=0.4641	1-0.4641=0.5359	0.5906*0.5359=0.3165
57-0.5* 2=56	55/56=0.9821	1-0.9821=0.0179	03165*0.0179=0.0057

9. Answer: a
   Answer e is incorrect because it is always possible to estimate survival time from a Kaplan-Meier survival curve when survival is greater than 50%. The extrapolation of the 50% cumulative survival in the vertical axis (ordinate) to the horizontal axis (abscissa) for those without a history of skin infection shows a median survival of 30 to 50 days. Thus answer a is correct and answers b, c and d are incorrect. Note that it is not possible to estimate the median survival of those with a skin infection history, because their survival in less than 50%.
10. Answer: b
    Answer a is incorrect because a low cumulative incidence is not an assumption of the Kaplan-Meier method. Answer c is incorrect because the Kaplan-Meier method, unlike the actuarial life table, is not based on intervals. Answer d is incorrect because it is inconsistent with the necessary assumption described in answer b, which is the correct answer.

CHAPTER 7

1. Answer: c
   The best answer is c. Since cases and controls are selected into the study by the investigator, it is difficult to directly calculate incidence rates using case and control data. The number of cases and controls is fixed by the investigator with only exposure proportion varying between the two groups. Therefore, the rate of the outcome in the exposed and nonexposed groups has been fixed by the investigator's control over the marginal totals of the study's 2×2 table. These fixed margins limit the ability of case-control studies to estimate incidence.
   Answer a is incorrect since it describes a key feature of well-conducted case-control studies. Answer b is incorrect as it defines the methodologic approach of the case-control study. Answer d describes an important limitation of case-control studies, especially those that rely on self-reported exposure histories.

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Answer e also presents a potential limitation of case-control studies when the outcome lacks clear clinical definitions

2. Answer: a
   The best answer is a. This study investigates the health status of selected population groups and assesses disease (cholera) and exposure (residence in a certain village defined by type of water supply) simultaneously. This is a defining feature of cross-sectional studies in that they are used to test the possible relationship between an exposure and a disease based on information collected at one point in time. The proportion of cholera carriers in each of the three villages can be compared in order to evaluate the association of water supply on transmission of cholera. However, the study's findings may be limited by inadequate information concerning prior exposure and residential mobility among the studied population.
   Answers b through e all present other epidemiologic study types that have been described in the text. If the study were a case-control design, then cases (cholera carriers) would be compared to controls with additional information about retrospective exposures. In the cohort study approaches, persons would be categorized by exposure to a specific water supply at a time when they were free of cholera, then followed either prospectively or retrospectively to determine if they became cholera carriers. Finally, an experimental study would involve assigning exposure (water supply) to persons and the ethical obligation to test methods to reduce cholera exposure.
3. Answer: c
   The best answer is c. The statement presents a concise definition of the methodology of the case-control study. Cases of a disease are identified based on a common set of diagnostic criteria. Once this group is determined, an adequate control group must be identified. This group should be representative of the population and have the potential to develop the outcome of interest. By comparing the histories for these two groups, factors or agents (i.e., exposures) which are found to be associated with the case group provide evidence of their effect on the health outcome.
   Answer a is incorrect as this statement describes surveillance studies using past disease rates in order to predict future trends. Answer b is incorrect as it describes a systematic review that seeks to combine evidence from multiple studies using various designs in order to fully review a potential association. Answer d is similar to a prospective cohort approach in which persons with a baseline exposure are followed over time to determine the health outcome. Finally, answer e is not correct because statement a does not describe a case-control study.
4. Answer: b
   The best answer is b. This study describes a prospective or concurrent cohort study. First, the study starts with a group of persons who belong to a specific population. Second, the population is divided into exposure groups at the baseline or origin of the study. In this example, 3,000 residents of Baltimore were recruited in 1965 and classified according to alcohol consumption patterns at that time. Finally, the study groups are followed over time to determine the development of specific diseases that are believed to be associated with the exposure of interest. If the rate of disease is higher in the exposed group, then a risk factor has been identified.
   Answer a is incorrect because a cross-sectional study would measure alcohol consumption and cancer at the same time, e.g., 1965, and evaluate the association based on this single data collection. Answer c is incorrect because the study is not retrospective. A retrospective study would start with the identification of a population similar to the example given, but exposure would be defined for a past time period using either subject recall or other records to determine the classification. In this example, if the study had started with outcome follow-up in 1981 and used records previously collected in 1965 to determine exposure categories, then it would be a retrospective cohort study. Answer d is incorrect. Clinical trials seek to test the outcomes associated with treatments intended to benefit persons so a study of alcohol and cancer would not be ethically compatible with this study design. Finally, answer e is incorrect as a case-control study would begin with the identification of cancer cases, the selection of a control group without cancer, and then exposure to alcohol in the past would be determined
5. Answer: c
   The best answer is c. This is a matched case-control study. Cases (women with uterine cancer) are identified and a control group (women without uterine cancer) is identified in order to facilitate comparison.

In this study, the controls are selected on the basis of matching for specific confounders that are associated with the outcome and with the exposure of interest, namely, age, race, weight, and parity.

Answer a is incorrect. This study design would start with women free of uterine cancer, determine exposure to estrogen, and then follow the cohort to determine who developed uterine cancer at a later date. Answer b shares many design features with the concurrent cohort study. The main difference is that the retrospective cohort study would start with disease follow-up and rely on past records of estrogen use in order to determine exposure. Answer d is incorrect because the study involves a past history of exposure rather than a single, simultaneous measure of exposure and uterine cancer. Finally, answer e is incorrect as the women are not assigned to estrogen exposure groups based on randomization or some other selection process

6. Answer: d

The best answer is d. This is a retrospective cohort study. It begins in 1977 and conducts follow-up for health outcomes through 1986; however, it relies on a past documentation of risk factors, namely, height and weight in 1935, to determine the exposure of the study subjects. Exposure was documented in the past and is assumed to have an influence on the development of coronary heart disease over 50 years later.

Answer a is incorrect since the study involves measures of exposure and disease over time. Answer b is incorrect because all subjects are assumed to be without coronary heart disease at enrollment in 1977. Answer c is incorrect because the study relies on past documentation of risk factors instead of a concurrent enrollment and determination of exposure groups prior to prospective follow-up. Finally, answer e is incorrect because study subjects have not been assigned to exposure groups at enrollment

7. Answer: e

The best answer is e. Statements a, c, and d describe characteristics of a case-control study design. The objective is to compare exposure proportions among cases with a disease and controls without disease as described in a. Further, the investigators can identify several comparison groups if they have reason to believe that risk is different on the basis of specific characteristics. For example, a case-control study of occupational-related lung cancer cases can have a control group selected from the general population, a second control group from a different occupational group, and a third control group from the same industry as the case group. Each of these control groups is representative of different source populations and allows for inference about the association between specific exposures such as occupational agents and lung cancer. Finally, statement d describes a common limitation of case-control studies, especially those that rely solely on subject-reported exposure histories. The awareness of case status may result in differential recall of rare or unique exposures for persons who are seeking an explanation for their ill health compared to those who are not ill.

Finally, answer b describes a cohort study approach, especially a prospective study that can be used to measure incidence rates of disease developing in persons followed over time. Therefore, this statement is the only one that does not reflect a case-control approach.

8. Answer: d

The best answer is d. In a case-crossover study, the selected population consists only of case subjects. Each individual case's exposure history is divided into periods that comprise case and control periods for comparison. The case-crossover design is typically described as an alternative form of a matched case-control study in which case subjects are self-matched and is also frequently described as a case-control adaptation of the crossover trial.

Answers a and b are incorrect since cohort studies, either prospective or retrospective designs, include only disease-free persons at the study start time. Those persons who develop the outcome prior to the end of follow-up are compared to other members of the cohort who do not experience the outcome at the end of follow-up. Answer c is incorrect because control subjects in a case-cohort are chosen from all members of the cohort with which the study began regardless of whether they eventually become cases during follow-up. Finally, answer e is incorrect because a case-control study includes subjects who are identified as a case or control prior to analyses being conducted.

9. Answer: c

10. Answer: c

Answers a and b are incorrect because matching for the very exposure one wants to evaluate would eliminate a

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possible association. Answers d and e are incorrect because initially sampling individuals according to presence or absence of a variable (tea drinking) that results in the exposure (tea metabolism biomarker) characterizes a cohort, not a case-control study. Thus answer c is the correct one. Note that the case-control study is the best design when the outcome is rare.

11. Answer: c
    Answer a is incorrect because the matching characteristics cannot be studied regardless of the prevalence of the disease. Answer b is incorrect because matching is a pre–data collection strategy that intrinsically adjusts for the variables that have been matched for; therefore matching precludes the need for adjustment of the variables that have been matched for (unless the categories of the matching variables are too broad, in which case additional adjustment for finer categories after data collection is needed to avoid residual confounding). Answer d is incorrect because both individual and frequency matching can use hospital and general population controls. Answer c is the best answer: the more variables are matched for, the more difficult it is to find an appropriate control for each case.

CHAPTER 8

1. Answer: d
   The best answer is d. An etiologic study is intended to assign a causative role to a factor associated with a disease. At the initiation of a basic cohort study, two groups of persons are designated from a source population: one includes persons exposed to the suspected factor, and the other includes persons not exposed to the suspected factor. Both groups are free of the disease at the beginning of the study. Moreover, both groups should be as similar as possible with regard to other factors that influence disease, e.g., distribution of age or tobacco smoking. At the end of the study observation period, a comparison of the incidence rates for each group can reveal the etiologic role of the suspected factor if exposure to it leads to an increased risk of disease. This inference is more likely to be determined as causal if other relevant factors associated with disease development are not different in the two populations. The role of potential confounding factors is discussed more fully later in the book.
   Statement a is incorrect since the two groups can be of different sizes. The goal is to calculate an estimate of disease risk, i.e., the incidence rate in both groups. Because the incidence rate is standardized by the total of each group, differences in sizes between the groups are not a problem. Statement b is incorrect as a cohort study must begin with all subjects free of disease. The groups are chosen based upon exposure to the suspected factor. Statement c is incorrect. Since we are concerned with the etiologic role of a suspected factor, then it may be necessary to select a source population that is not representative of the general population. For example, we may select a source population of persons of a specific age or susceptibility to the disease. Although etiologic inferences are improved by statements of generalizability to the larger population, this is not required in order to conclude that a suspected factor is biologically causative. Statement e is incorrect by ruling out b and c.
2. Answer: a
   The best answer is a. A prospective cohort study design typically requires larger study groups, longer follow-up, and more resources than a case-control study. Due to its design, it is well suited for precise exposure measurement since each study group is defined by the subjects' exposure status. Further, a prospective cohort study records new cases of disease developing in a study group and thus gives an estimate of the incidence of disease. Since the study starts with disease-free subjects at entry, it is not likely that recall of relevant characteristics and exposures would be different between the two study groups. Since b, c, and d are advantages of the cohort study design, these answers are incorrect
3. Answer: c
   The best answer is c. Retrospective cohort designs differ very little from prospective designs in terms of study groups, risk estimates, and sample sizes (refer to text). The main difference is that retrospective cohort study designs use information collected prior to the investigator commencing the study, usually for determining exposure status.
   Statements a and b are incorrect as they describe essential design features of all cohort studies. Statement d is incorrect as it contrasts with the correct answer c. Since both types of cohort study designs start with a source population that is classified by

exposure status, an adequate sample size in each study group is necessary to ensure the occurrence of a sufficient number of outcomes for measures of incidence. Statement e is incorrect since cohort studies are best suited for studying rare exposures (refer to text).

4. Answer: a
   The best answer is a. The lack of randomization between the study groups means that a different factor associated with the disease may influence the assignment of exposure groups. This factor could influence the initial selection of persons or lead to differential classification of subjects to exposure groups, especially if it is associated with the exposure. Such a factor would qualify as a potential confounder of the exposure–disease relationship (refer to text).
   Statements b and c are incorrect because, although lack of randomization can lead to unequal proportions of exposed and unexposed, this is not a major problem. Cohort studies that do not randomize successfully reach adequate balance in proportions of exposed and unexposed. Statement d has no bearing on cohort studies since the duration of the study is determined by the investigator and is typically influenced by the amount of time necessary to observe an adequate number of disease events. Statement e has no bearing on cohort studies as exposure status is typically a fixed characteristic that is not expected to change for the duration of the study.
5. Answer: c
   The best answer is c. A prospective cohort study that begins with a source population enables the investigator to determine a greater variety of exposure groups among the study subjects. Each of these exposure groups can be followed over time for disease incidence and then compared relative to one another. This would likely lengthen the duration of the study as subjects must have the opportunity to become exposed to the factor of interest during the study period. In addition, they must be at risk for development of the disease. Of course, different scenarios can be imagined that would allow us to imagine the necessary time of observation for exposure and disease; however, the opportunity for study subjects to become exposed to a variety of factors would be an advantage of starting with an exposure-free population.
   Statement a is incorrect. In fact, the opposite is more likely. Since subjects must become exposed and then develop disease, it is probable that the study will take longer to complete. Statement b is incorrect because all cohort studies have the ability to study a diverse set of outcomes. Starting with an unexposed source population would not change this feature. Statement d is wrong for the same reason that a is incorrect. This would likely increase the study costs. Statement e is incorrect as a and d have both been eliminated as correct responses
6. Answer: d
   Answer a is incorrect because cases within a defined cohort were not compared with cohort individuals who had not died from cancer. Answer b is incorrect because there was follow-up from 1948 to 1968 through 2010 and cross-sectional studies are based on a sample selected at a given point in time with no follow-up. Answer c is incorrect because individuals were not followed concurrently from 2010 on (i.e., from the time when the study started). Answer e is incorrect because the investigators did not start the study by selecting cases and controls. Answer d is correct: the investigators used data on the exposure (obesity) that had been collected when individuals attended the university in 1948 through 1968 and followed these individuals from 1948 to 1968 (past) through 2010 (when the study started). This type of design is also known as nonconcurrent cohort study.
7. Answer: b
   Answer a is incorrect because in a case-cohort study, cases are compared with a sample of the total baseline cohort (not just noncases). Because cases were compared with controls, this is not a retrospective cohort study, and thus answer c is incorrect. Because cases were identified during follow-up, this is not a cross-sectional study based on a single point in time; thus answer d is incorrect. Given the lack of randomization (which would have been impossible, given that an inflammatory marker cannot be randomly allocated), this is not a randomized clinical trial; thus answer e is incorrect. This is a nested case-control study, comparing cases that developed during follow-up with noncase controls, making answer b the correct one.

CHAPTERS 10 AND 11

1. Answer: e
   The best answer is e. Randomization in a clinical trial seeks to make assignment a nonpredictable event,

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especially in regard to characteristics that may confound the relationship between the exposure and the health outcome. It is intended to remove selection bias by the investigators, either conscious or unconscious, that would create study groups defined by certain factors such as improved prognosis, improved compliance with treatment, or better baseline health status. Also, random assignment attempts to make exposure groups similar in regard to attributes such as age, sex, race, and other potential confounders.

Answer a is incorrect since it is the selection of study subjects at enrollment which ensures representativeness. Answer b is an approach to randomization but it is not a necessary component. Randomization can be an unblinded process with investigators and subjects aware of exposure assignment. Answer c is incorrect because randomization has no impact on later measurement of outcomes. Answer d is incorrect because randomization can fail. This is akin to the concept that a coin can be flipped 10 times and still result in all heads. This may lead to differences in baseline characteristics between the study groups.

2. Answer: e

The best answer is e. There is no information of the baseline rate of recovery from sore throat for comparison to the medicine's performance. If 100% of persons are expected to recover from a sore throat in 4 days, then in theory, the medicine has a worse prognosis. A key concept in epidemiology is the relative comparison of two groups that are assumed to differ by specific characteristics such as exposure or treatment with a medicine. Without a comparison group, proportions have little information about the relative risk or improvement for health outcomes.

Answer a is not correct because the claim is incorrect. Answer b is incorrect because a rate is presented assuming that all subjects were followed from a common baseline period. Answer c is incorrect because there is no reason to suspect that the study cohort has a long-term change in risk associated with sore throat, an acute health outcome. Finally, answer d is incorrect because a claim of effectiveness can be made without a statistical test. Results that are subjected to statistical tests are assumed to have more certainty than those are not; however, this is not a requirement for evaluation.

3. Answer: c

The best answer is c. By blinding both observer and subject, the investigator hopes to reduce many common forms of bias associated with clinical trials. For example, knowledge of exposure group may lead observers to differentially classify outcomes in study subjects. Also, if study subjects are aware of their treatment group, they may change their approach to other important factors such as diet, exercise, or smoking that could have an impact on disease.

Answer a is incorrect because comparability is ensured by selection and randomization processes, not blinding. Answer b is not correct because blinding has no effect on sampling variation. Answers d and e are not correct because they include only one part of the correct answer, the reduction of observer or subject bias, without the second blinded group being mentioned.

4. Answer: b

The best answer is b. A one-sided statistical test is preferred for precision when the direction of the risk is known. It reduces the uncertainty of the test for exposure-disease relationships that are known to be associated in a specific direction. For example, when studies have demonstrated that an exposure increases risk for a disease, such as estrogen use and endometrial cancer, subsequent studies seeking to more precisely quantify the extent of risk can improve precision by testing the association in a single specified direction.

Answer a is not correct as this assumption underlies both one- and two-sided power calculations. Answer c is not correct. This statement concerns a potential dose-response model in which the association differs based upon level of exposure rather than a single test of association between exposure and nonexposure. Answer d is incorrect because a one-sided test does not eliminate Type II error more than Type I error but it can increase the efficiency of statistical tests recognizing these errors. Finally, answer e does not apply to the conditions for a one-sided test. These tests can be applied even when multiple control groups are included in a study.

5. Answer: b

The best answer is b. A crossover trial assumes that there is no carryover of exposure when subjects are assigned to a subsequent exposure group. Residual exposure effects would bias the measure of association between the second exposure and the health outcome since the first exposure assignment would still have influence on the disease. Therefore, this condition is a requirement for crossover trials.

Answer a is incorrect because there still may be order effects in specific cases of multiple exposures, for example, when the planned crossover involves multiple treatments. Answer c is incorrect because a crossover trial does not necessarily require stratified randomization. This approach can help reduce potential selection bias but it is not always essential for valid study results from randomized trials. Answer d is incorrect. These characteristics are important at all times in any clinical trial. Even with crossover assignment, compliance must be ensured to avoid potential misclassification biases. Answer e is not correct because a crossover trial has no impact on the enrollment of study subjects who are representative of the population. This characteristic must be emphasized during recruitment and enrollment even prior to exposure assignment, regardless of whether it is a single assignment or a crossover trial.

6. Answer: a
   The best answer is a. According to the definition of Type I error, this error occurs when the study concludes that a difference exists between two treatments when the truth is that they are not different. Even if statistical tests imply that a strong difference exists between the two drugs, this difference may not be associated with a difference in efficacy, but may occur by chance alone. By concluding that the treatments are different, the investigator is making a Type I error. Answer b is not correct as a Type II error occurs when a study concludes that the treatments are not different, when in reality they are different. This error usually results from insufficiently powered studies that do not include adequate numbers of subjects to detect the difference in the two treatments. Answer c is a false answer as 1 minus alpha would indicate that the investigators concluded the G Answer d is the expression for the power of the study, i.e., its ability to detect a difference assuming that one truly exists. This is related to Type II error rather than Type I error and, given the reality that the two treatments differ, Type II error is not applicable. Answer e is not correct as one of the choices was applicable.
7. Answer: c
   The best answer is c. Well-conducted clinical trials provide the best level of evidence for inferences regarding health outcomes. By using randomization it is likely that the study groups are similar in terms of other important characteristics and that the distribution of these characteristics is the same in both groups (answer a). Further, randomization seeks to eliminate selection bias either by enrolled subjects (answer b) or by the investigators (answers d and e). This leaves answer c as a potential limitation of clinical trials. In fact, since clinical trials are focused on specific questions, usually concerning treatment, they are conducted with specifically targeted study groups who may not be representative of the population as a whole. Further, many trials may exclude the most severely ill persons due to ethical concerns. By limiting enrollment to subjects who have a specific definition for study eligibility, the clinical trial may have limited external validity when the results are applied to a more general population including all ages, races, and levels of disease severity. Therefore, answer c is correct.
8. Answer:
   The answer is 57. Using the table provided, the two measures of importance are the lower of the two cure rates and the differences in the two cure rates. In this example, the lower cure rate is estimated to be 25%. Starting at this row in the table, the number of patients needed for each study group is found by identifying the column that estimates the difference in the two cure rates; in this example the difference is 25%. Since the table is calculated assuming an alpha of 0.05 and a beta of 0.20, the number needed for each study group is 57.
9. Answer:
   The answers are as follows:
   - 9a: the design that allows comparing differences in prevalence is **b**.
   - 9b: for rare diseases, **c** is the best design.
   - 9c: for evaluation of the effectiveness of smoking cessation plus nicotine patches, **e** is the ideal design.
   - 9d: **d** is the best design, given that health outcomes of heavy drinking are relatively common
   - 9e: air pollution is an ecological exposure and thus **a** is the design of choice.
10. Answer:
    Using the intention to treat strategy, all individuals randomized to the new drug are compared with those randomized to standard care, regardless of whether there were cross-overs. Thus, the cumulative incidence ratio is $[(10+ 20) \div 150] \div [(5 + 40) \div 150] = 0.67$.

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11. Answer:
A per protocol analysis is an interpretation of randomized clinical trial results that removes data from patients who didn't comply with the protocol. Compare group 1: 10/90 (those who took drug A as assigned) to group 2: 40/130 (those who received standard of care as assigned). These are the persons that took the drug per protocol. (10/90)/(40/130) = 0.36

CHAPTER 12

1. Answer:
The answer is 15.2. The relative risk equals the rate of disease in the exposed group divided by the rate of disease in the nonexposed group. In this study the exposed group is comprised of those who received childhood radiation therapy. The nonexposed group is comprised of those who did not receive childhood radiation therapy. The disease of interest is benign thyroid tumor.
The rate of disease in the exposed group is:

$$= \frac{\text{52 developed a benign thyroid tumor in the exposed group}}{\text{2,872 persons in the exposed group}}$$

$$= 0.0181$$

The rate of disease in the nonexposed group is:

$$= \frac{\text{6 developed a benign thyroid tumor in the nonexposed group}}{\text{5,055 persons in the nonexposed group}}$$

$$= 0.0012$$

The relative risk is then calculated by dividing the rate of benign thyroid tumors in the exposed by the rate in the nonexposed group:

$$= \frac{0.0181}{0.0012}$$

$$= 15.2$$

2. Answer: d
The best answer is d. The estimated relative risk for this small matched pairs study is calculated using the matched odds ratio approach. That is, only discordant pairs of cases and controls are of interest. In this study, there are 6 women with uterine cancer who were estrogen users matched to 6 controls who were not estrogen users. Conversely, there are 2 controls who reported using estrogen matched to 2 cases who were not estrogen users.
The ratio of discordant matched pairs

$$= \frac{\text{The number of pairs in which the case is exposed, control not exposed}}{\text{The number of pairs in which the control is exposed, case not exposed}}$$

$$= \frac{6}{2}$$

$$= 3.0$$

Thus, the estimated relative risk is equal to 3.0.
The following 2×2 table can also be drawn to assist in the matched odds ratio calculation:

	CONTROLS	
Cases	**Estrogen User**	**Estrogen Nonuser**
Estrogen User	2	6
Estrogen Non User	2	2

Answers a, b, c, and e are incorrect because the calculation is incorrect. Answer b is incorrect but could result if the relative risk was inverted such that the exposed control, nonexposed case pairs were in the numerator. However, this approach is not consistent with the tested hypothesis, i.e., that exposure is associated with uterine cancer. Answer c could only be correct if there were an equal number of pairs with discordant classifications. The inference would be that there is no association between estrogen use and uterine cancer. Finally, answer e is not correct because it reflects an incorrect calculation with an overestimate of the relative risk.

3. Answer: e
The best answer is e. By unmatching the pairs, a 2×2 table can be completed in which all 24 women (12 cases and 12 controls) are stratified by exposure status. In this study, there were 8 cases who were exposed and 4 cases who were nonexposed. Among the 12 controls, 4 were exposed and 8 were not exposed.

Using the cross-tabulation approach to calculate the unmatched odds ratio to estimate the relative risk:

$$= \frac{ad}{bc}$$

$$= \frac{8*8}{4*4}$$

$$= 4.0$$

Thus, the estimated relative risk is 4.0.

	Uterine Cancer	Control
Estrogen User	8	4
Estrogen Nonuser	4	8

Answers a, b, c, and d are incorrect because the calculation is incorrect. Answer a is incorrect as it assumes that estrogen use is more likely to be reported by controls rather than cases. Answers b through d are incorrect as they are underestimates of the unmatched relative risk as calculated above.

4. Answer: e
The best answer is e. The interpretation for a relative risk equal to 1 is that the disease is not associated with the exposure of interest. A ratio (relative risk) of 1 means the disease is equally likely in both the exposed and nonexposed groups. The interpretation for a relative risk less than 1 in the disease is more likely in the nonexposed persons compared to the exposed persons. A ratio (relative risk) less than 1 means the exposure is inferred to be "protective" of the outcome.
Answer a is incorrect because it applies only to a relative risk of 1 and does not support the interpretation of relative risks less than 1. Answer b is not correct because it does not support the inference for a relative risk estimate of 1. Answer c is incorrect because no information about matching or randomization is presented in the question. Answer d is incorrect because no information was provided about the control group so it is not possible to evaluate the validity of the relative risk.

5. Answer:
The answer is 4.5. The matched pairs odds ratio is equal to the ratio of the discordant pairs in which the case is exposed divided by the number of discordant pairs in which the control is exposed. In this example, smoking 1+ pack per day is considered to be exposed relative to smoking less than 1 pack per day. There are 36 matched pairs in which the case is exposed, control nonexposed, divided by 8 pairs in which the control is exposed and the case is nonexposed per the study definition.
Using the matched odds ratio approach:

$$= \frac{\text{The number of pairs in which the case is exposed, control not exposed}}{\text{The number of pairs in which the control is exposed, case not exposed}}$$

$$= \frac{36}{8}$$

$$= 4.5$$

Thus, the odds ratio is 4.5. The 2×2 table presented in this question is set up for matched data and can be used directly to assist this calculation.

6. Answer:
The answer is 6.3. To break the matching, all cases and controls are considered as individuals and entered into a 2×2 table that comprises one cell each for exposed cases (38), nonexposed cases (42), exposed controls (10), and nonexposed controls (70) (see 2×2 table below). It is worth noting that these numbers can be found in the margins of the matched pairs table.
Using the cross-tabulation approach to calculating the unmatched odds ratio:

$$= \frac{ad}{bc}$$

$$= \frac{38*70}{10*42}$$

$$= 6.3$$

Thus, the odds ratio is 6.3.

	Death	Control
Smoking 1+ pack/day	38	10
Smoking<1 pack/day	42	70

7. Answer:
The answer is 1:7 (0.143). The odds of exposure among controls equals the number of exposed controls (10)

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divided by the number of unexposed ocntrols (70). This reduces to a ratio of 1 to 7. Dividing the two numbers gives an odds that controls smote 1+ pack/day of 0.143.

8. Answer: e

The best answer is e. The relative risk for each age stratum can be calculated by divinding the mean annual incidence of ASHD in men by the mean annual incidence of ASHD in women. Going down the table, the estimated relative risks are:

	Men	Women	
Age at Beginning of Study (yrs)	**Yearly Follow-up Exams (Mean Annual Incidence)**	**Yearly Follow-up Exams (Mean Annual Incidence**	**Relative Risk**
29-34	19.4	0.0	19.4/0.0= ∞
35-44	40.0	2.1	40.0/2.1 = 19.0
45-54	106.5	29.4	106.5/29.4= 3.6
55-62	209.1	117.8	209.1/117.8 = 1.8

Even though the relative risk of ASHD is higher in men compared to women for each age group, the magnitude of the increased risk is lowest in the oldest age group due to a greater increase in the mean annual incidence of ASHD in women.

Answer a is incorrect because the relative risks are different in each age stratum.

Answer b is incorrect because the relative risk is lowest in the oldest age group.

Answer c is incorrect because the relative risk is infinite in the youngest age group due to the lack of outcomes of ASHD among younger women. Answer d is incorrect because the relative risk declines with age group.

9. Answer: e

The best answer is e. The initial (baseline) exam measures the prevalence of ASHD in the sex-stratified age groups. It is assumed that all persons reporting ASHD at baseline are excluded from subsequent follow-up for the outcome during the study. Therefore, the mean annual incidence measures the rate of new cases during a year in each group. As expected, prevalence and incidence rates of ASHD are highest in the oldest age group of each sex; however, at younger ages, men are more likely to have prevalent ASHD and to develop incident ASHD.

Answer a is incorrect because the statement does not explain the reason for the differences in the rates at initial examination and during follow-up. Even though the statement is true, it does not address the question posed. Answer b is incorrect because no data are presented that would permit the calculation of the case-fatality rate. Answer c is not correct because the statement is generic and does not explain the stark differences in the prevalence and incidence rates per 10,000 persons. Finally, answer d is not correct because no information is presented that corresponds with an ability to evaluate the claim.

10. Answer:

In an individually matched case-control study, the odds ratio is the ratio of discrepant pairs. In the table, it is 31 ÷ 16 = 1.9. Note that this ratio is equivalent to the ratio of the number of pairs favoring the hypothesis (exposed cases and unexposed controls) to the number of pairs against the hypothesis (unexposed cases and exposed controls).

11. Answer:

The odds ratio in an unmatched study is calculated as the odds of exposure in cases divided by the odds of exposure in controls; thus, the odds ratio in this table is [(198 ÷ 177) ÷ (174 ÷ 233) = 1.5]. Note that when the table is set up exactly as the table above ("exposed" in the upper row and "cases" in the left hand side column), the odds ratio can be calculated as the 'cross-product' ratio: [(198 × 233) ÷ (174 × 177) = 1.5].

12. Answer:

Because the odds ratio of exposure and the odds ratio of disease are mathematically the same, the interpretation of the odds ratio is "prospective": the odds of prostate cancer in those never using aspirin is 1.5 times greater than the odds in those ever using aspirin.

13. Answer:

Relative risk (when the incidence of the disease is low), prevalence of exposure in the source population (using prevalence in the control group), odds ratios

of disease and exposure can be all estimated in a case-control study (answers **a**, **c**, **d** and **e**). However, incidence rate is not available in a case-control study; thus, **b** is the right answer.

CHAPTER 13

1. Answer: b
   The best answer is b. This percentage is an attributable risk as it measures the amount of lung cancer due to cigarette smoking. Attributable risks are typically presented as percentage measures as they indicate the proportion of the disease that is manifest by the risk factor under study as the exposure.
   Answer a is incorrect because an incidence rate measures the number of cases of a disease developing in a population during a specific time interval. Its units are typically in units applicable to rates such as cases per 1,000 persons. Answer c is incorrect since a relative risk compares the risk of disease in one group with the risk in a separate group and is a unitless measure. Answer di is incorrect because a prevalence risk is a misnomer and does not refer to a standard epidemiologic measure. Finally, answer e is incorrect because a proportionate mortality ratio measures the number of deaths from a disease relative to all deaths in the population. Though this measure is a proportion and can be expressed as a percentage, the example here does not provide information about all deaths in the population.
2. Answer:
   The answer is 27.5/1,000 (or 27.5 per 1,000 persons). This is found by calculating the standard incidence of coronary heart disease (CHD) in smokers and then subtracting the background incidence of CHD in the nonexposed (persons who do not smoke).
   More specifically:
   Incidence of CHD among smokers (exposed)

$$= \frac{65 \text{ cases}}{2{,}000 \text{ exposed persons}}$$

$$= 0.0325 * 1{,}000$$

$$= 32.5 \text{ cases per } 1{,}000 \text{ persons}$$

   Baseline incidence in nonsmokers (unexposed)

$$= \frac{20 \text{ cases}}{4{,}000 \text{ unexposed persons}}$$

$$= 0.0050 * 1{,}000$$

$$= 5.0 \text{ cases per } 1{,}000 \text{ persons}$$

   To calculate the incidence rate of CHD attributable to smoking, take the difference between the exposed group incidence rate and the baseline incidence rate:

$$= 32.5 \text{ cases per } 1{,}000 - 5.0 \text{ cases per } 1{,}000 \text{ persons}$$

$$= 27.5 \text{ cases per } 1{,}000 \text{ persons}$$

   Thus, the attributable incidence rate is 27.5 cases per 1,000 persons.
3. Answer:
   The answer is 84.6%. This estimate is found by taking the aforementioned difference, 27.50 per 1,000, and dividing it by the incidence in the exposed group:

$$= \frac{0.00275}{0.00325}$$

$$= 0.8462$$

   Thus, the proportion of CHD in smokers that is attributable to smoking is 84.6%. This calculation assumes that there is a background risk of CHD that affects persons who choose to smoke as well as those who do not. However, the very high proportion of attributable risk due to exposure clearly implicates the role that cigarette smoking plays in CHD risk.
4. Answer:
   The answer is 3.6/1,000 (or 3.6 per 1,000 persons). First, the incidence in the total population must be calculated. This rate is a weighted average of the incidence rate in the exposed and nonexposed populations. It can only be calculated when the proportion of exposure is known for the population of interest. In this example, the incidence rate of lung cancer in smokers was 9 per 1,000 and 45% of the population were smokers. The incidence rate of lung cancer for nonsmokers was 1 per 1,000 with the remaining 55% of the population considered nonexposed. The incidence rate of lung cancer in the total population is therefore equal to the rate in smokers multiplied by the proportion of smokers in the population plus the rate in nonsmokers multiplied by the proportion of nonsmokers in the population:

$$= (0.009 * 0.45) + (0.001 * 0.55)$$

$$= 0.0046 * 1{,}000$$

$$= 4.6 \text{ per } 1{,}000$$

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Thus, the incidence rate of lung cancer attributable to smoking is 3.6 per 1,000.

5. Answer:
   The answer is 78.3%. In order to convert the total population attributable incidence rate to a proportion, the incidence in the total population less the baseline incidence must be divided by the incidence in the total population. Per the calculation in question 4, the incidence rate of lung cancer in the total population is 4.6 per 1,000 (or 0.0046). The baseline (nonexposed) incidence rate given in question 4 is 1 per 1,000 (or 0.001):

$$= \frac{0.0046 - 0.001}{0.0046}$$

$$= 0.7826$$

$$= 0.7826$$

   Thus, the proportion of incidence of lung cancer attributable to smoking is 78.3%.

CHAPTER 14

1. Answer: c
   The best answer is c. The conclusion is incorrect because the diagnosis of diabetes was made at the pancreatic cancer diagnosis. No prior information is given for a record of diabetes in advance of the biologic onset of pancreatic cancer. Since pancreatic cancer affects many of the same organs and biologic mechanisms that are impacted by diabetes, it is reasonable to assume that the two diseases are correlated and the one may have induced the other. Without a clear distinction in terms of diagnostic dates, the failure to establish temporality undermines the causal assumption.
   Answer a is incorrect since the conclusion is erroneous. Answer b is incorrect because there is a matched control group described. Answers d and e are incorrect because there is likely to be nondifferential diagnosis of diabetes in both case and control groups. Since diabetes is a disease with a clear set of clinical indicators, it is not likely that either group has differential ascertainment.
2. Answer: a
   The best answer is a. There are many other risk factors that could explain the cause of fetal death. The experience of sexual intercourse in the month prior to delivery is an ambiguous indicator that would need further evaluation prior to assigning it a causal association with the outcome.
   Answer b is incorrect because there is a comparison group in this retrospective cohort study, i.e., women who did not have sexual intercourse in the month preceding deliver. Answer c is incorrect because the study does report incidence rates. Answer d is incorrect because no information is given (i.e., confidence intervals) that allows for the evaluation of statistical significance. In fact, with 27,000 women in the study, the high rate of outcomes (11% vs. 2.5%) implies that there are at least over 3,000 outcomes. This clearly suggests a strong statistical significance based on the large sample size. Answer e is incorrect because answers b and c are both incorrect.
3. Answer: e
   The best answer is e. This is not a criterion of causality as described in the text or in the classic references for causal criteria, namely, the 1964 Surgeon General's report as cited in the chapter on Sir Austin Bradford Hill's speech on causal criteria published in 1965. Answers a through d are incorrect as all are examples of causal criteria described in the text.
4. Answer: b
   The best answer is b. Since the disease never occurs without Factor X, it is by definition necessary. However, exposure to only Factor X does not lead to disease since either Factor A, B, or C must be present. This means that Factor X alone is not sufficient to cause disease.
   Answer a is incorrect. Although exposure to Factor X is necessary, it is not sufficient because Factor X alone is not followed by the disease. Answer c is also incorrect since we have established that exposure to Factor X is necessary due to its presence in all cases of the disease. Answers d and e are incorrect because the necessity of exposure to Factor X has been established.
5. Answer: d
   The best answer is d. Factor A is present in some cases of the disease but always with exposure to Factor X. However, if Factor A were completely removed, the disease would still manifest through the combined actions of exposure to Factor B or C and Factor X. This means that Factor A is neither necessary nor sufficient for the disease to develop.
   Answers a through c are incorrect because it is determined above that Factor A is neither necessary nor

sufficient. Finally, answer e is incorrect as there is a correct answer d available in the choices.

CHAPTER 15

1. Answer: e
   The best answer is e. All of the listed approaches are suitable for the control of potential confounders. As discussed in this chapter as well as the chapter on case-control studies, individual matching (answer a) and group matching (answer c) are approaches used in the design of a study that remove potential confounding by eliminating any differences in the comparison groups for the matched factor. Alternatively, confounding can be controlled in the analytic phase after study design and data collection. Two commonly used techniques are stratification (answer b) and adjustment (answer d). Stratification involves creating categories of a potential confounder and conducting statistical analyses using only data from persons within specific categories, or strata, of the confounder. Adjustment is typically performed using regression modeling in which the specified outcome and exposure model include additional variables that represent the confounders. A detailed description of this approach is beyond the scope of the text but is commonly practiced by epidemiologists.
2. Answer: c
   Stratification (answer **a**), adjustment (including regression modeling) (answers **b** and **d**) are strategies that can be applied only after data collection ends and the database is ready for analysis. Restriction, however (answer **c**) is used at the design stage by narrowing the inclusion criteria in such a way that the groups to be compared – for example, cases and controls – are matched for the criteria variables. For example, in a case control study, only Hispanic women aged 40-49 of at least 12 years of education are included. Thus, for these variables, cases and controls are matched.
3. Answer: c
   The best answer is c. The issue of bias is introduced when it is noted that a specific group is evaluated differently than another. In this question women who use oral contraceptives are evaluated differently than women who do not. Bias is defined as the distortion in the effect measure observed in a study due to systematic error in the design, conduct, or analysis. In this question, five types of bias are listed. The most likely type of bias attributable to increased observation of certain individuals in a study based on a common characteristic is surveillance bias. In effect, the reported association between phlebitis (or inflammation of a vein) and oral contraceptive use could be due to increased scrutiny for the outcome phlebitis) by physicians who are aware of exposure to oral contraceptives among their patients.
   Answer a is incorrect. Selection bias refers to bias due to the method in which individuals are included in a study. In this question, no such methodologic approach is discussed. Answer b refers to interviewer bias, a type of information bias. This bias generally describes systematic errors attributable to the approaches to data collection taken by interviewers who are aware of specific characteristics of an individual. In this example, no interview process is mentioned so this answer is incorrect. Answer d, nonresponse bias, is a form of selection bias that relates to the lack of data from specific individuals potentially eligible for a study that are not invited or do not choose to participate in a study. If individuals who do not participate in a study have a common characteristic that is associated with their lack of response, then this bias is relevant. In the question, however, no such circumstance is presented. Finally, answer e, recall bias, is a form of information bias in which study subjects recall information, usually past exposures in a differential manner. The most common form of this is the increased reporting of rare or unique exposures by persons who have a disease (i.e., cases) because they are seeking a justification for their adverse health. This form of bias is not relevant to the example given in the question.
4. Answer:
   The answer is 12. An additive model of interaction deals with attributable risks. The data presented in the table list the observed rates of disease from Factor A and Factor B.
   The upper left cell of the table is the baseline rate for persons without either factor. Among those without Factor B, the rate increases by 4 for those with exporue to Factor A (7 less baseline rate of 3 results in an increase of 4 for Factor A). Conversely, among those without Factor A, the rate increases by 5 for those with Factor B (same calculation approach as

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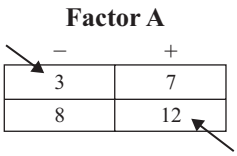
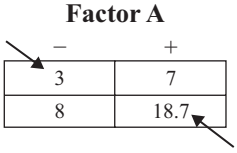
with Factor A, in this instance the rate increases from 3 to 8 with exposure to Factor B). Therefore, the additive interaction model assumes that exposure to both Factor A and Factor B increases the rate of disease by the sum of the individual increases. Thus, persons positive for both factors have an increased rate of 4 plus 5 which equals 9. The final cell in the table has the rate value of 12 since the increase of 9 for exposure to both factors is added to the baseline rate of 3.



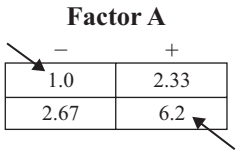
5. Answer:
The answer is 18.7. Using a multiplicative model for interaction means that we are interested in relative risks. Again, the baseline, or referent, group is the cell with a rate of disease by 2.33 (7 divided by baseline rate 3). Exposure to only Factor B increases the rate by 2.67 (8 divided by baseline rate 3). Therefore, the multiplicative model of interaction estimates the rate for exposure to both factors to be equal to the product of the increased rates for each factor multiplied by the baseline rate. In this example, $2.67 \times 2.33 \times 3 = 18.7$



6. Answer:
The answer is 9. First, the rates of disease in the table must be converted to attributable risks assuming an additive model. First, the referent group (no exposed to either Factor A or Factor B) has a baseline rate of 3 for the disease. This is set to zero by definition since the attributable risk for neither exposure is zero. For those exposed to Factor A only (Factor B is negative) the upper right corner value is 4 (7 less the baseline rate of 3). Moreover, the lower left corner of the table equals 5 (8 less the baseline rate of 3). Using the additive model of interaction, the two rates are summed to produce the attributable risk for the lower right corner. In this example 4 plus 5 equals 9.



7. Answer:
The answer is 6.2. First, the rates of disease must be converted to relative risks to complete the multiplicative table. In this instance, the referent group is set to a value of 1. Therefore, for those exposed to Factor A only, the relative risk in the upper right corner should be 2.33 (7 divided by 3). Meanwhile, for those exposed to Factor B only, the relative risk is 2.67 (8 divided by 3). To find the relative risk assuming multiplicative interaction of Factor A and Factor B, the two relative risks are multiplied, thus 2.33 times 2.67 is 6.2.



8. Answer:
The best answer is d. The poor execution of the study notwithstanding, the one source of bias not applicable here is bias due to loss of control subjects. The study started with 100 controls who were admitted to the same hospital at the same time as the cases; however, these individuals had hernias, a disease not expected to share risk factors with thyroid cancer. No loss of study subjects was mentioned so it is unlikely that bias due to loss to follow-up has affected the reported results.
Answer a is not correct because recall bias is potentially likely since cases were interviewed and will probably recall past x-ray exposures due to their thyroid cancer diagnosis. Answer b is not correct because hospital-based controls are not representative of the general population which includes a substantial proportion of healthy, nonhospitalized persons. This study chooses controls from persons admitted to the hospital with a specific diagnosis, hernia, therefore the controls could have common characteristics that are not likely to be found among the cases or the general population. This would introduce bias. Answer c is also a likely source of bias because cases were interviewed for history of x-rays in addition to medical record review, but controls were not interviewed, so ascertainment of

x-ray exposure relied solely on medical record review. Finally, answer e is also probable since persons with cancer may be different than those with hernia on the basis of past exposure to x-ray therapy.

9. Answer: b

The best answer is b. The bias will influence the risk estimate. Assuming that there is an association between sweetener use and bladder cancer, then the selection of controls who aso have a high likelihood of sweetener use due to obesity related conditions would dilute the risk estimate and reduce its value. Therefore, the observed risk will be an underestimate of the true risk due to this dilution of exposure differences between the bladder cancer and obesity-related-conditions groups.

Answer a is not likely since this answer posits that no bias is introduced by the selection criterion. Answers c and e are not correct because adequate information exists to predict the direction of the bias. Though more information is always helpful, enough has been provided to answer the question. Since b and answer d are contradictory, one must be incorrect. Since the question implies that controls will also have high rates of exposure to artificial sweeteners, any association reported will likely underestimate risk rather than overestimate it. To visualize this, create a 2×2 table and assume 100 cases (50% exposed) and 100 controls (20% exposed) (see Table 1 below). This table gives an odds ratio of 4.0. Now, increase the exposure among controls only, so that 30% are exposed (see Table 2 below). This table gives an odds ratio of 2.3. The risk estimate (odds ratio) will continue to decrease as more controls are exposed. This simple example illustrates the selection bias inherent to this example that is introduced by selecting controls with a higher likelihood of exposure than a representative group of persons without bladder cancer.

TABLE 1

	Bladder Cancer	No Bladder Cancer
Sweetener use	50	20
No sweetener use	50	80
Totals	100	100

TABLE 2 **Increase the Exposure among the Controls Only**

	Bladder Cancer	No Bladder Cancer
Sweetener use	50	30
No sweetener use	50	70
Totals	100	100

Odds ratio of bladder cancer comparing sweetener users to no-sweetener users:

$$= \frac{ad}{bc}$$

$$= \frac{50*80}{20*50}$$

$$= 4.0$$

Table 2 Increase the Exposure among the Controls Only

Odds ratio of bladder cancer comparing sweetener users to no-sweetener users:

$$= \frac{ad}{bc}$$

$$= \frac{50*70}{30*50}$$

$$= 2.3$$

CHAPTER 16

1. Answer: c

The best answer is c. In twin studies, concordance is a measure of the number of twin pairs who are similar in terms of disease profile. This is more typical with monozygotic twins who share identical genes. It is noted in the text that a high level of concordance implies that the disease is likely genetic; however, the text also notes that there may be a nonhereditary, or environmental, contribution. This is due to the increased likelihood that monozygotic twins also share many of the same environmental factors, especially during childhood, making it difficult to clearly indicate whether a disease is genetic or environmental in origin when concordance is observed in monozygotic

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twins. Answer c best captures this combination of explanations and is the correct answer.

Statement a is incorrect because increased concordance among monozygotic twin pairs definitely implicates a genetic cause of the disease. Statement b is incorrect because of the difficulty in clearly indicating whether hereditary or environmental factors were the sole force due to similar environmental exposures of twins as discussed in the text. Statement d is incorrect. Increased concordance favors a genetic cause but does not eliminate an environmental cause and does not indicate equality in environmental and genetic factors. Finally, statement e is factually incorrect. Because monozygotic twins share 100% of the same genetic material, it is impossible for monozygotic twins to have gender differences.

2. Answer: c

The best answer is c. Marital status of the biologic parents is immaterial to the disease risk factors being studied. The information presented implies that the incidence of a disease can be compared between both biologic and adoptive relatives to identify potential genetic risk factors. The assumption would be that similar incidence rates in biologic, but not adoptive, relatives would strengthen the case for a genetic cause. Meanwhile, the opposite finding (i.e., similar disease incidence patterns in adopted children and adoptive siblings) would suggest environmental factors.

When studying this hypothesis, age of onset (answer a) is an important characteristic of the disease risk, just as it is in most studies. Also, contact with biologic parents (answer b) is relevant since it implies potential confounding of the association measure. Selection factors concerning adoption are important to disease risk (answer d). Many disease-related characteristics could serve to reduce the likelihood of a child being adopted if the characteristics are present or known. This would introduce selection bias in studies of adopted and biologic relatives. Finally, answer e is ruled out since answer d is a relevant concern.

3. Answer: b

The best answer is b. In this example, the concordance rates are highest in persons with identical genes (monozygotic or identical twins). There is also a dose-response relationship manifested from nonrelatives (husband-wife) who share many environmental risk factors, to moderately genetically related persons (parent-child, dizygotic twins, and nontwin siblings), through to identical twins. This relationship is more indicative of a potentially important genetic contribution of disease as described in statement b.

Answer a is an incorrect inference from these observations. The dose-response relationship is quite clear based on the rates in genetically related persons, making genetic factors important in the etiology of schizophrenia. Answer c is incorrect because no data are presented for incidence. The only numbers reported are concordance rates within various pairs of relatives. Additionally, no information is available to describe the number of cases occurring in the population during a specific interval. Answer d is incorrect for a similar reason to answer c. No data are presented for the number of cases of schizophrenia in the population. Finally, statement e is incorrect because the presented findings do not denote risk. More specifically, no relative measures of association are presented for twin status and development of schizophrenia, thus answer (e) cannot be evaluated.

4. Answer: b

The best answer is b. The standardized mortality ratio (SMR) is a measure of association in which a value of 100 indicates that the observed numbers of deaths from a disease are equal to the expected number (i.e., 100 is the null value). These data show that migrant subgroups of the Japanese population have similar SMRs. This would indicate that environmental factors do not contribute substantially to disease mortality. Therefore, genetic factors are the major determinants.

Answer a is incorrect because the SMRs would be expected to differ by migrant status if environmental factors are the major determinants of disease mortality. This is also the reason why answer c is incorrect. The similar risk estimates for native Japanese, Japanese migrants, and children of Japanese ancestry indicate migrants and children kept similar cultural habits of their native ancestors. Statement d may be relevant to the interpretation of disease rates in migrant studies, but fails to describe the similar SMRs among native Japanese, migrants, and children of ancestors presented in the table. If there was a selection effect for migrants, then one would anticipate that their SMR would be lower relative to the nonselected persons remaining in Japan. Finally, statement e cannot be judged on the basis of the information presented.

5. Answer: c
   The best answer is c. If an association is detected then it is evident that genetic factors contribute to disease risk. The actual proportion of attributable risk would rely on other factors, such as the percentage of the population considered "exposed," i.e. having the allele that is associated with the disease.
   Answer a is incorrect since association does not indicate causation. Other explanations for an association must be considered prior to concluding that the disease is clearly caused by a gene. Answer b is incorrect because the answer implies that the population proportion attributable risk is 100%. This is not implied by the question, which states that only an *association* with incidence has been detected. Answer d is incorrect because it would be premature to eliminate environmental factors on the basis of the information given. Finally, answer e is incorrect because it assumes information about the clinical expression of the disease that is not addressed in the question.

CHAPTER 17

1. Answer: b
   The best answer is b. Studies that evaluate process of medical care focus on measurable factors such as the provision of health care or the delivery of services. This type of metric specifically avoids evaluating the impact of health services on treated populations. With this in mind, the proportion of patients with complications from a disease is not measured by process techniques.
   Answer a is specifically cited in the text as an example of a process measure. It involves the provision of health care to a population, in this case patients receiving blood pressure measurements. Answer c also measures process. The number of patients advised to stop this behavior is a process of health care intervention. Answer d is similar to a in that services are being provided that aid in the clinical detail known about patients. Finally, answer e is also a process measure since it involves an administrative approach to providing affordable, quality health care to individuals.
2. Answer: a
   The best answer is a. In this instance, the question asks for an evaluation metric used in experimental conditions. This fits the definition of efficacy (answer a) as described in the annotated answer for question 3. See the annotation for question 3 for further discussion on why answers c through e are incorrect.
3. Answer: b
   The best answer is b. Effectiveness is defined in the text as the evaluation of health care services in the population at large, or the community-dwelling population. This differs from efficacy (answer a), which stipulates that the service is measured in a study or experimental setting. Answer c is incorrect since effect modification is associated with the interaction of risk factors and disease risk measures. Answer d applies to cost-benefit analyses that compare different service options to determine which one has the greatest impact relative to its resource utilization. Finally, answer e is incorrect due to b.
4. Answer: d
   The best answer is d. Evaluating health care services is a time-dependent process. When comparing outcomes from different periods, investigators must be aware of secular changes in disease risk and mortality. If information is available that suggests that mortality is decreasing over time, then a study which compares recent periods with past historical periods has a built-in bias. In this example, the most probable explanation for a change in mortality rate, specifically, the case-fatality rate (CFR), has to do with changes in other risk and survival factors over time, rather than the influence of the health service.
   Answer a is incorrect because a change in prevalence could also suggest a decreased number of cases which could result in an increased CFR after provision of the health service was started. Answer b is not correct for the same reason. Moreover, incidence rates have little to do with CFR calculations which rely on the ratio of deceased to all prevalent cases. Answer c is not correct since the new health service is assumed to *directly* affect the CFR. Finally, answer e is not correct due to statement d.
5. Answer: d
   The best answer is d. The installation of a Coronary Care Unit (CCU) implies that more severe disease will be treated by this hospital. In this example, there is a definite change in the disease severity distribution of patients from the non-CCU to the CCU period. In the non-CCU period, 60% of the patients had mild coronary disease while very few (4%) were in shock on arrival at the hospital. With the arrival of the CCU,

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the disease severity of the patients increased. In the CCU period, only 10% of patients had mild coronary heart disease, while both severe and shock patients increased. Given the distribution of these numbers, it is very difficult to compare the non-CCU and CCU periods in terms of treatment effectiveness since the study populations are representative of two different groups of disease severity.

Answer a is not correct due to answer d. Answer b is not correct since case-fatality rates (CFRs) are a type of mortality rate and in this study are best suited to measuring mortality since the ratio reflects only persons with coronary heart diseases. Answer (c) is incorrect because no information is given to evaluate referral patterns in either period. Finally, answer e is incorrect because there is little reason to believe that the study spanned a long enough period of time for secular changes in the myocardial infarction (MI) rate. If anything, these data suggest that MI has gotten more severe in the later period based on the classification of disease severity among patients.

CHAPTER 18

1. Answer: a

   The best answer is a. As the screening program is effective at diagnosing cancer Z at an earlier stage, the number of identified cases will increase in the first year. With no change in the course of the disease (i.e., duration), this initial increase in diagnosed cases will increase the incidence rate of cancer Z due to the addition of these cases identified at an earlier stage.

   The other two answers b and c are incorrect if one follows the reasoning described above. Both of these responses fail to adequately describe the impact of the initial surge of cases on the incidence rate of cancer Z during the first year of the screening program.

2. Answer: a

   The best answer is a. Consistent with the answer above, one must recall that prevalence is equal to incidence times duration of disease. Following the reasoning above, if incidence increases during the first year with no change in the duration of the disease, then prevalence, being the product of these two, must also increase.

$$\text{Prevalence} = \text{incidence} * \text{duration}$$

$$\text{Prevalence} = \text{increase} * \text{no change}$$

$$\text{Prevalence} = \text{increase}$$

   Again, the other two answers b and c are inconsistent with the relationship between increasing incidence and prevalence during the first year of the screening program as described above.

3. Answer: b

   The best answer is b. In this instance, it is established that there will be an increase in incidence and prevalence of cases of cancer Z during the first year of the screening program. The case-fatality rate (CFR) is the ratio of the number of disease-specific deaths occurring during a specific time interval among all prevalent cases of the disease. Assuming no change in the course of the disease, then the denominator of the CFR will increase while the numerator should stay the same. This will dilute the CFR during the initial year of the screening program.

$$\text{CFR} = \frac{\text{Number of cancer Z} - \text{specific deaths}}{\text{Number of all prevalent cases of cancer Z}}$$

$$= \frac{\text{No change}}{\text{Increase}}$$

$$= \text{A decrease in the CFR}$$

   The other two answers a and c are incompatible with the reasoning described above.

4. Answer: c

   The best answer is c. The mortality rate for cancer Z measures the number of persons dying from cancer Z divided by the total population at risk. In this scenario, these numbers will not change with the institution of the screening program since it is assumed that the course of cancer Z will not change. Given the same number of expected deaths from cancer Z divided by the same approximate population, then the mortality rate will remain constant and not change due to the screening program.

$$\text{Mortality rate} = \frac{\text{Number of persons dying from cancer Z}}{\text{Total population at risk}}$$

$$= \frac{\text{No change}}{\text{No change}}$$

$$= \text{No change}$$

Both answers a and b are incorrect since each maintains a directional change in the mortality rate for cancer Z.

5. Answer: b
   The best answer is b. The objective of an early detection program is to identify disease at a clinical stage during which it can be more effectively treated. Breast cancer is a disease that definitely progresses through early stages after biologic onset, and it is responsive to early treatment options including chemotherapy, radiation therapy, and surgical interventions such as removal of the breast. A program that identifies breast cancer at a stage when tumors are small and noninvasive should have better results for survival due to earlier treatment. Of all the answers listed, b best expresses this goal. By identifying breast cancer at earlier, treatable stages, long-term survival rates should increase after adjustment for lead time.
   Answer a is incorrect because it deals with proportionate mortality measures which are influenced not only by breast cancer but also by the other diseases that constitute the other mortality proportions. Further, mortality rates for breast cancer are also dependent on the number of identified cases, not just the survival of prevalent cases. This answer is not ideal. Answer c is wrong because incidence rates are not an adequate measure for evaluating an early detection program. In fact, a declining incidence rate over 15 years would have other explanations besides early detection through screening. For a disease such as breast cancer, decreases in the incidence rate would have more to do with reduction in risk factors rather than early detection of clinical cases. Answer d is wrong because prevalence is an estimate of the number of cases in a population at risk. For the same reasons as those listed for incidence, prevalence should not change due to earlier detection. It is most likely that prevalence would increase, even over a 15-year period, with an effective screening program. Answer e is incorrect because answer b is correct
6. Answer: c
   The correct answer is c. Screening programs work best when they can identify diseases that are reduced in severity following early diagnosis and treatment. When a disease is susceptible to medical intervention and treatment, then a screening program is most effective.
   Answer a is not correct because diseases with low prevalence would make poor candidates for a screening program. If there are not many cases of the disease to detect in a screened population, then most of the resources employed by the screening program will not recoup a benefit. Answer b is also incorrect because a low case-fatality rate (CFR) indicates that the course of the disease is not severe. Again, a screening program may make an impact on the disease, but the pre-existing low CFR will not indicate that there has been effective reduction in disease severity with the use of a screening program. Finally, answer d is incorrect because the disease is assumed to be readily diagnosed (this implies that screening is similarly effective to clinical diagnosis). Further, if treatment efficacy has been shown to be equivocal (i.e., not having a significant impact) from clinical trials, then the identification of cases of the disease with a screening program does not entail a large impact in treatment and reduction of disease severity. Finally, answer e is not correct due to c.
7. Answer: b
   The correct answer is b. The critical point in disease detection is a point in the natural history of disease before which treatment is more effective and/or less difficult to administer than it would be if the disease is diagnosed at the usual time after symptoms have appeared. In order for early detection to be beneficial, there must be a critical point before the usual time of diagnosis (C). The critical point would therefore have to lie in the interval between the earliest time at which the disease can be diagnosed (B) and the usual time of diagnosis (C) that follows the manifestation of clinical symptoms. By intervening to move the detection point closer to (B), the screening program is designed to make treatment of the patient possible at an earlier stage of the disease when the treatment will presumably be easier and more effective.
   Answer a) is incorrect because it is assumed that disease cannot be detected at any time prior to (B). Answer c is incorrect because point (C) is the time at which a case is usually diagnosed. A screening program that detects disease after this period adds little, since the person is likely to seek care during this time even if there is no screening. Answers d and e are incorrect following the reasoning applied to answer a.
8. Answer: c
   The correct answer is c. The question asks for an outcome that is not useful as an indicator of screening benefits. Incidence of a disease most likely will

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increase with the implementation of early detection screening programs, so a noted reduction in the incidence rate of the disease, especially during early years, may spuriously indicate the screening program is ineffective.

Answer a describes a condition that is a favorable result of early detection screening programs. By identifying more cases of disease at an earlier period, the case-fatality rate should decrease with either a reduction in the numerator or an increase in the denominator, or a combination of both. This same reasoning applies to statement b as well. Again, early detection should decrease severity, mainly mortality, from a disease. Answer d is also a useful evaluation for an early disease detection program. By diagnosing disease at an early stage, other adverse health effects should not result if the cases receive treatment. Finally, statement e is not correct because it describes the ideal measure of the effectiveness of an early treatment program. Since disease screening will not eliminate a case of a disease, its benefit arises from earlier and more sensitive diagnosis of those with the disease. An assumption of early detection is that treatment can reduce disease severity. Moreover, the screened population should enjoy an overall increase in quality of life since the benefit of the screening program also extends to persons who are negative for the disease but gain peace of mind when this status is verified.

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