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 Death¹

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



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.

‡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.)

[†]Uterus refers to uterine cervix and uterine corpus combined.



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:

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

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:

```
Annual mortality rate from all causes
for children younger than 10 years of
age (per 1,000 population) =
No. of deaths from all causes in
1 year in children younger than 10 years
of age
No of children in the population
younger than 10 years of age at midyear
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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 *causespecific rate*. For example, if we are interested in mortality from lung cancer, we would calculate it in the following manner:

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:

Annual mortality rate from leukemia in children <10 years of age (per 1,000 population) = No. of deaths from leukemia in 1 year <u>in children <10 years of age</u> No. of children in the population <10 years of age at midyear

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:

Case - fatality (%) =

No. of individuals dying during a specified $\frac{\text{period of time after disease onset or diagnosis}}{\text{No. of individuals with the specified disease}} \times 100$

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 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 Mortality rate from disease $X = \frac{18}{100,000} = 0.00018$, or 0.18% Case-fatality from disease $X = \frac{18}{20} = 0.9$, 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:

Proportionate mortality from cardiovascular diseases in the US in 2014 (%) = No. of deaths from cardiovascular diseases in the US in 2014 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

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

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

	E	ARLY 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.



"Know what? The days get longer at the same time the nights get shorter."

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 Proporti	onate 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



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. WISQARSTM 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.)



¹Rates 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.)

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



^aRates 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

10		U.S. STA	NDARD CERTIFICAT	E OF DEATH	ST	TE FILE NO		
	1. DECEDENT'S LEGAL NAME (Include AKA's i	f any) (First, Middle, Last)		2. SEX	3. SOCIAL SECUR	TY NUMBER		
	4a. AGE-Last Birthday (Years) 4b. UNDER 1 YEAR Months Days	4c. UNDER 1 DAY Hours Minutes	5. DATE OF BIRTH (Mole	ay/Yr) 6. BIRTH	PLACE (City and Sta	te or Foreign Countr	ry)	
	7a. RESIDENCE-STATE	7b. COUNTY	71	2. CITY OR TOW	'N			
	7d. STREET AND NUMBER	7e. AP1	r. NO. 7f. ZIP CODE		7g.	INSIDE CITY LIMI	TS? 🗆 Yes 🗆	No
	8. EVER IN US ARMED FORCES? 9. MARIT. Yes No Married	AL STATUS AT TIME OF Married, but separa Dever Married U	DEATH 11 Ited DWidowed Jnknown	D. SURVIVING S	POUSE'S NAME (If	wife, give name pric	or to first marriage	e)
I By:	11. FATHER'S NAME (First, Middle, Last)			12. MOTHER'S	NAME PRIOR TO F	IRST MARRIAGE (I	First, Middle, Las	t)
V Verified ECTOR:	13a. INFORMANT'S NAME 13b. RI	ELATIONSHIP TO DECE	EDENT	13c. MAILING A	ADDRESS (Street an	d Number, City, Stat	te, Zip Code)	
L DIR	IE DEATH OCCURRED IN A HOSPITAL	14. PLACE OF DEA	TH (Check only one: see in	Istructions)	FR THAN & HOSPIT	۵1 -		
FUNERA	Inpatient D Emergency Room/Outpatient In Second Control Contro Control Control Contro	Dead on Arrival (& number) 16.	Hospice facility Dursing CITY OR TOWN, STATE, A	home/Long term	care facility Deci	dent's home 🗆 Ot	ther (Specify): 17. COUNTY OF	DEATH
-	18. METHOD OF DISPOSITION: Burial D Donation Entombment Removal from	Cremation 19. PL State	LACE OF DISPOSITION (Na	ame of cemetery,	crematory, other plac	e)		
	20. LOCATION-CITY, TOWN, AND STATE	21. NAM	E AND COMPLETE ADDRI	ESS OF FUNERA	L FACILITY			
	22. SIGNATURE OF FUNERAL SERVICE LICEN	ISEE OR OTHER AGEN	т			23. L	ICENSE NUMBE	ER (Of Licensee)
	ITEMS 24-28 MUST BE COMPLETE		24 DATE PRONOUN	CED DEAD (Mo/	Dav/Yr)		25 TIME PE	RONOLINCED DEA
	WHO PRONOUNCES OR CERTIFIE	S DEATH			,,			
	26. SIGNATURE OF PERSON PRONOUNCING	DEATH (Only when appl	licable) 2	7. LICENSE NUM	IBER	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 CORONER CO	L EXAMINER OR ONTACTED?	res ⊡ No
	32. PART I. Enter the <u>chain of events</u> —disease arrest, respiratory arrest, or ventricular fibril lines if necessary.	SE OF DEATH (Se s, injuries, or complication lation without showing the	e instructions and e nsthat directly caused the e etiology. DO NOT ABBRE	examples) death. DO NOT (VIATE. Enter on	enter terminal events ly one cause on a lin	such as cardiac e. Add additional		Approximate interval: Onset to death
	IMMEDIATE CAUSE (Final disease or condition> a	Due to /c						
	Sequentially list conditions, b	Due to (c	n as a consequence on.					
	listed on line a. Enter the UNDERLYING CAUSE c	Due to (c	or as a consequence of):					
	(disease or injury that initiated the events resulting in death) LAST d.	Due to (or as a consequence of):					
	PART II. Enter other significant conditions contrib	uting to death but not res	sulting in the underlying cause	se given in PART	I	33. WAS AN AU	TOPSY PERFOR	MED?
						34. WERE AUTO	res □ No DPSY FINDINGS	AVAILABLE TO
žfi	35. DID TOBACCO USE CONTRIBUTE 36. TO DEATH? 36.	IF FEMALE:	st vear		37. MANNER OF D	EATH	CAUSE OF DE	ATH? U Tes U No
ERTIFI	Yes Probably	Pregnant at time of deal	ath		Natural F	omicide		
CAL CI	No Unknown	Not pregnant, but preg	nant within 42 days of death		Accident F	ending Investigation	n	
MEDI		Not pregnant, but pregnant,	nant 43 days to 1 year befor	e death			ilou	
	38. DATE OF INJURY 39. TIME OF INJU	Unknown if pregnant v JRY 40. PLACE	within the past year OF INJURY (e.g., Deceden	t's home; constru	ction site; restaurant;	wooded area)	41. INJU	RY AT WORK?
	(Mo/Day/Yr) (Spell Month)						ا ت	res ⊡ No
	42. LOCATION OF INJURY: State: Street & Number:		City or Town:	Apartment	No.:	Zip Code:		
	43. DESCRIBE HOW INJURY OCCURRED:					44. IF TRANSP	ORTATION INJU tor	JRY, SPECIFY:
						Passenger Pedestrian Other (Specif	fv)	
	45. CERTIFIER (Check only one): Certifying physician-To the best of my know	ledge, death occurred du	ue to the cause(s) and mann	er stated.		C Outer (opcon	37	
	 Pronouncing & Certifying physician-To the b Medical Examiner/Coroner-On the basis of e 	est of my knowledge, de xamination, and/or invest	ath occurred at the time, dai igation, in my opinion, death	te, and place, and occurred at the tir	I due to the cause(s) ne, date, a nd place	and manner stated. , and due to the cau	use(s) and manne	er stated.
	46. NAME, ADDRESS, AND ZIP CODE OF PER	SON COMPLETING CAU	ISE OF DEATH (Item 32)					
	47. TITLE OF CERTIFIER 48. LICENSE NUM	IBER 49.	DATE CERTIFIED (Mo/Da	y/Yr)	50.	FOR REGISTRAR	ONLY- DATE FI	ILED (Mo/Day/Yr)
	51. DECEDENT'S EDUCATION-Check the box that best describes the highest degree or level of	52. DECEDENT OF H that best describe	ISPANIC ORIGIN? Check s whether the decedent is	the box	53. DECEDENT'S I decedent consid	RACE (Check one of lered himself or here	or more races to i self to be)	ndicate what the
	school completed at the time of death.	Spanish/Hispanic/I decedent is not Sp	Latino. Check the "No" box anish/Hispanic/Latino.	if	 White Black or African 	American		
	9th - 12th grade; no diploma	No, not Spanish/His	spanic/Latino		 American Indian (Name of the en Asian Indian 	or Alaska Native rolled or principal tril	be)	
ц В Д	High school graduate or GED completed Some college credit, but no degree	 Yes, Mexican, Mexi 	ican American, Chicano		Chinese Filipino Japanese			
leted	Associate degree (e.g., AA, AS)	Yes, Puerto Rican			 Korean Vietnamese Othera Asian (Craw 	- 16.3		
RALD	 Bachelor's degree (e.g., BA, AB, BS) 	 Yes, Cuban 			 Orner Asian (Spi Native Hawaiian Guamanian or C 	hamorro		
To Be FUNE	 Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA) Destructs (c.g., DED, EdD) as 	 Yes, other Spanish (Specify) 	/Hispanic/Latino		 Samoan Other Pacific Isla Other (Specify)_ 	inder (Specify)		
	 Dectorate (e.g., PnD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD) 							
	54. DECEDENT'S USUAL OCCUPATION (Indica	te type of work done dur	ing most of working life. DO	NOT USE RETIR	IED).			
l I	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.)

32. PART I. Enter the <u>chain or</u> arrest, respiratory arrest, o lines if necessary.	CAUSE OF DEATH (See instructions and examples) <u>events</u> -diseases, injuries, or complications-that directly caused the death. DO NOT enter terminal events such as cardiac ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional	Approximate interval: Onset to death		
IMMEDIATE CAUSE (Final disease or condition>	a Rupture of myocardium	Mins		
resulting in death) Sequentially list conditions.	Due to (or as a consequence of): Acute myocardial infarction	6 days		
if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE	Chronic ischemic heart disease	5 years		
(disease or injury that initiated the events resulting in death) LAST	Due to (or as a consequence of):			
PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I 33. WAS AN AUTOPSY PERFORM				
Diabetes, Chronic obstructive pulmonary disease, smoking				

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.)



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								
	N	UMBER OF D	EATHS		Sa			
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												
			1–4	5–14	15–24	25–34	35–44	45–54	55–64	65–74	75-84	>85
Race	All Ages	<1 Yea	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

^aAge-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 P	ERIOD	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	

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.

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 dea in the standar	ths expected d population:	2,238		1,830		
Age-adjusted ra	ites:	"Early" = $\frac{2,238}{1,800,000}$ =	= 124.3	"Later" = $\frac{1,830}{1,800,000}$ =	=101.7	

TABLE 4.9 Hypothetical Example of Direct Age Adjustment: III, Carrying Out an Age

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).

TABLE 4.10	Hypothetical C	omputation of	f a Standardized	I Mortality	Ratio (SMR)	for C	Disease
X for White W	orkers Ages 20	-59 Years, 2023	3				

	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	$3 = 1 \times 2$	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
	SMR (for 20- to 59	$P-\text{year-olds} = \frac{406}{138.8} \times 100 = 292$	2	

The SMR is defined as follows:

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

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.

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

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

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

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,



High income countries Low income countries

Fig. 4.22 Selected causes of disease burden by low- versus high-income countries, 2015. *DALYs,* Disabilityadjusted 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.)

TABL	E 4.14 Global Health Estimates	2019: 20 Leadin	g 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

- **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 ratese. 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:

		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	

Annual Cancer Deaths in White Male Workers in Two Industries

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:

	COI	MMUNITY 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	

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

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