## 1.2 ANALYSIS OF AGE, BIRTH COHORT, AND PERIOD EFFECTS

Health surveys conducted in population samples usually include participants over a broad age range. Age is a strong risk factor for many health outcomes and is also frequently associated with numerous exposures. Thus, even if the effect of age is not among the primary objectives of the study, given its potential confounding effects, it is often important to assess its relationship with exposures and outcomes.

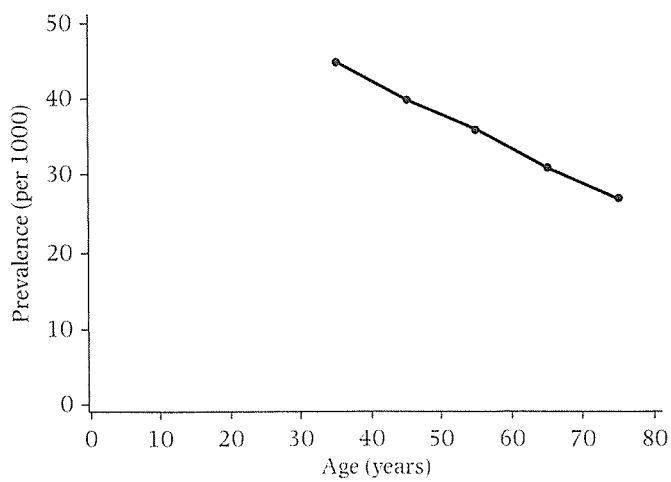
Table 1-1 shows the results of a hypothetical cross-sectional study conducted in 2005 to assess the prevalence rates of a disease Y according to age. (A more strict use of the term "rate" as a measure of the occurrence of incident events is defined in Section 2.2.2. This term is also widely used in a less precise sense to refer to proportions such as prevalence.[1] It is in this more general sense that the term is used here and in other parts of the book.)

In Figure 1-1, these results are plotted at the midpoints of 10-year age groups (e.g., for ages 30–39, at 35 years; for ages 40–49, at 45 years; and so on). These data show that the prevalence of Y in this population decreases with age. Does this mean that the prevalence rates of Y decrease as individuals age? Not necessarily. For many disease processes,

**TABLE 1-1** Hypothetical data from a cross-sectional study of prevalence of disease Y in a population, by age, 2005.

| Age group (years) | Midpoint (years) | 2005 Prevalence (per 1000) |
|---|---|---|
| 30–39 | 35 | 45 |
| 40–49 | 45 | 40 |
| 50–59 | 55 | 36 |
| 60–69 | 65 | 31 |
| 70–79 | 75 | 27 |

**FIGURE 1-1** Hypothetical data from a cross-sectional study of prevalence of disease Y in a population, by age, 2005 (based on data from Table 1-1).



exposures have cumulative effects that are expressed over long periods of time. Long latency periods and cumulative effects characterize, for example, numerous exposure/disease associations, including smoking-lung cancer, radiation-thyroid cancer, and saturated fat intake-atherosclerotic disease. Thus, the health status of a person who is 50 years old at the time of the survey may be partially dependent on this person's past exposures (e.g., smoking during early adulthood). Variability of past exposures across successive generations (birth cohorts*) can distort the apparent associations between age and health outcomes that are observed at any given point in time. This concept can be illustrated as follows.

Suppose that the same investigator who collected the data shown in Table 1-1 is able to recover data from previous surveys conducted in the same population in 1975, 1985, and 1995. The resulting data, presented in Table 1-2 and Figure 1-2, show consistent trends of decreasing prevalence of Y with age in each of these surveys. Consider now plotting these data using a different approach, as shown in Figure 1-3. The dots in Figure 1-3 are at the same places as in Figure 1-2, except that the lines are connected by *birth cohort* (the 2005 survey data are also plotted in Figure 1-3). Each of the dotted lines represents a birth cohort converging to the 2005 survey. For example, the "youngest" age point in the 2005 cross-sectional curve represents the rate of disease Y for individuals aged 30 to 39 years (average of 35 years) who were born between 1965 and 1974—that is, in 1970 on average (the "1970 birth cohort"). Individuals in this 1970 birth cohort were on average 10 years younger—that is, 25 years of age at the time of the 1995 survey and 15 years of age at the time of the 1985 survey. The line for the 1970 birth cohort thus represents how the prevalence of Y changes with increasing age for individuals born, on average, in 1970. Evidently, the cohort pattern shown in Figure 1-3 is very different from that suggested by the cross-sectional data and is consistent for all birth cohorts shown in Figure 1-3 in that it suggests that the prevalence of Y actually

**TABLE 1-2** Hypothetical data from a series of cross-sectional studies of prevalence of disease Y in a population, by age and survey date (calendar time), 1975–2005

| Age group (years) | Midpoint (years) | Survey date | | | |
|---|---|---|---|---|---|
| | | 1975 | 1985 | 1995 | 2005 |
| | | *Prevalence (per 1000)* | | | |
| 10–19 | 15 | 17 | 28 | | |
| 20–29 | 25 | 14 | 23 | 35 | |
| 30–39 | 35 | 12 | 19 | 30 | 45 |
| 40–49 | 45 | 10 | 18 | 26 | 40 |
| 50–59 | 55 | | 15 | 22 | 36 |
| 60–69 | 65 | | | 20 | 31 |
| 70–79 | 75 | | | | 27 |

*Birth cohort: From Latin *cohors*, warriors, the 10th part of a legion. The component of the population born during a particular period and identified by period of birth so that its characteristics (e.g., causes of death and numbers still living) can be ascertained as it enters successive time and age periods.[1]

**FIGURE 1-2** Hypothetical data from a series of cross-sectional studies of prevalence of disease Y (per 1000) in a population, by age, and survey date (calendar time), 1975, 1985, 1995, and 2005 (based on data from Table 1-2).

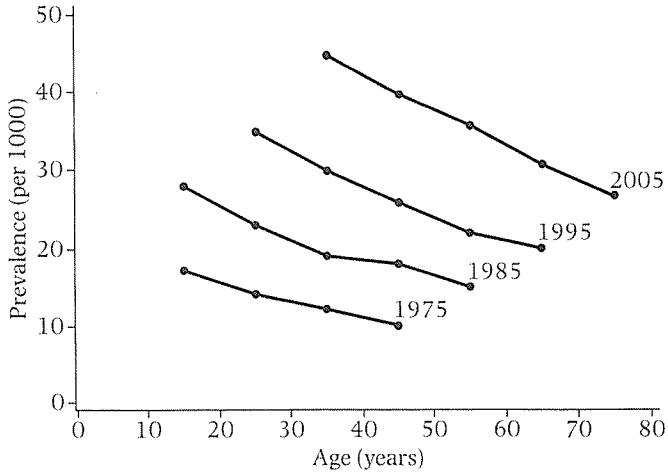
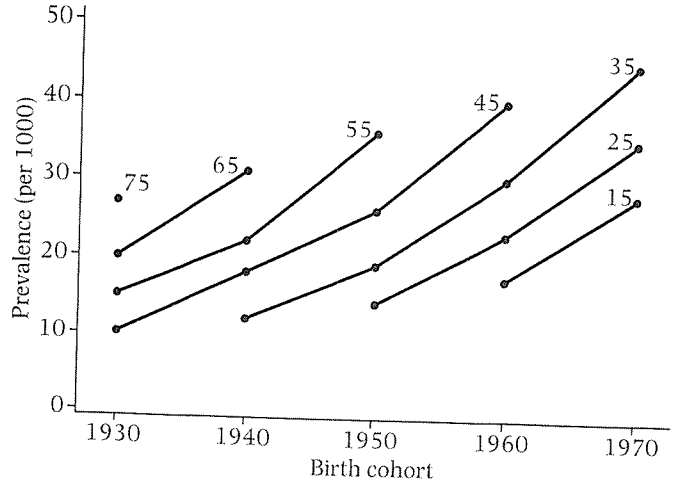



**FIGURE 1-3** Plotting of the data in Figure 1-2 by birth cohort (see also Table 1-3). The dotted lines represent the different birth cohorts (from 1930 to 1970) as they converge to the 2005 cross-sectional survey (solid line, as in Figure 1-1).


*increases* as people age. The fact that the inverse trend is observed in the cross-sectional data is due to a strong "cohort effect" in this example; that is, the prevalence of Y is strongly determined by the year of birth of the person. For any given age, the prevalence rate is higher in younger (more recent) than in older cohorts. Thus, in the 2005 cross-sectional survey (Figure 1-1), the older subjects come from birth cohorts with relatively lower rates, whereas the youngest come from the cohorts with higher rates. This can be seen clearly in Figure 1-3 by selecting one age (e.g., 45 years) and observing that the rate is lowest for the 1930 birth cohort, and increases for each subsequent birth cohort (i.e., the 1940, 1950, and 1960 cohorts, respectively).

**FIGURE 1-4** Alternative display of the data in Figures 1-2 and 1-3. Birth cohorts are represented in the *x* axis. The lines represent age groups (labeled using the midpoints, in years).




Although the cross-sectional analysis of prevalence rates in this example gives a distorted view of the disease behavior as a birth cohort ages, it is still useful for planning purposes; this is because, regardless of the mix of birth cohorts, cross-sectional data inform the public health authorities about the burden of disease as it exists currently (e.g., the age distribution of disease Y in 2005).

An alternative display of the data from Table 1-2 is shown in Figure 1-4. Instead of age (as in Figures 1-1 to 1-3), the scale in the abscissa (*x* axis) corresponds to the birth cohort and each line to an age group; thus, the slope of the lines represents the change across birth cohorts for a given age group.

Often the choice among these alternative graphical representations is a matter of personal preference (i.e., which pattern the investigator wishes to emphasize). Whereas Figure 1-4 shows trends according to birth cohorts more explicitly (e.g., for any given age group, there is an increasing prevalence from older to more recent cohorts), Figure 1-3 has an intuitive appeal in that each line represents a birth cohort as it ages. As long as one pays careful attention to the labeling of the graph, any of these displays is appropriate to identify age and birth cohort patterns. The same patterns displayed in Figures 1-3 and 1-4 can be seen in Table 1-2, moving downward to examine cross-sectional trends and diagonally from left to right to examine birth cohort trends. An alternative and somewhat more readable display of the same data for the purpose of detecting trends according to birth cohort is shown in Table 1-3, which allows the examination of trends according to age ("age effect") within each birth cohort (horizontal lines in Table 1-3). Additionally, and in agreement with Figure 1-4, Table 1-3 shows how prevalence rates increase from older to more recent cohorts (cohort effect)—readily visualized by moving one's eyes from the top to the bottom of each age group column in Table 1-3.

Thus, the data in the previous example are simultaneously affected by two strong effects: "cohort effect" and "age effect" (for definitions, see Exhibit 1-1). These two trends are jointly responsible for the seemingly paradoxical trend observed in the cross-sectional analyses in this hypothetical example (Figures 1-1 and 1-2), in which the rates seem

**TABLE 1-3** Rearrangement of the data shown in Table 1-2 by birth cohort.

| | | Age group (midpoint, in years) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Birth cohort range** | **Midpoint** | **15** | **25** | **35** | **45** | **55** | **65** | **75** |
| | | | | *Prevalence (per 1000)* | | | | |
| 1925–1934 | 1930 | | | | 10 | 15 | 20 | 27 |
| 1935–1944 | 1940 | | | 12 | 18 | 22 | 31 | |
| 1945–1954 | 1950 | | 14 | 19 | 26 | 36 | | |
| 1955–1964 | 1960 | 17 | 23 | 30 | 40 | | | |
| 1965–1974 | 1970 | 28 | 35 | 45 | | | | |

**EXHIBIT 1-1** Definitions of age, cohort, and period effects.

| | |
|---|---|
| Age effect: | Change in the rate of a condition according to age, irrespective of birth cohort and calendar time |
| Cohort effect: | Change in the rate of a condition according to year of birth, irrespective of age and calendar time |
| Period effect: | Change in the rate of a condition affecting an entire population at some point in time, irrespective of age and birth cohort |

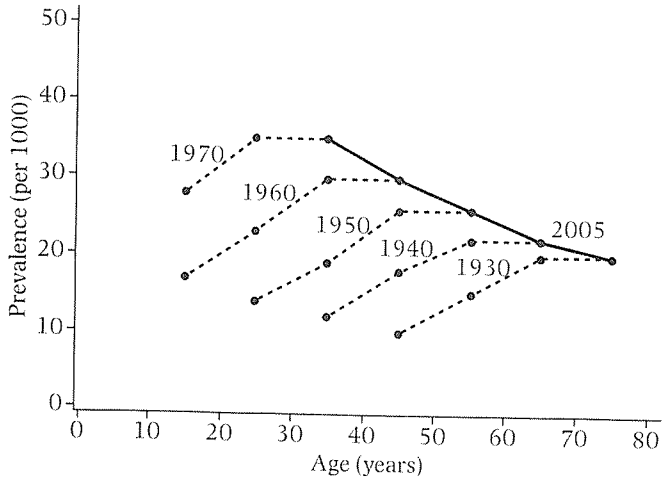
to *decrease* with age. The fact that more recent cohorts have substantially higher rates (cohort effect) overwhelms the increase in prevalence associated with age and explains the observed cross-sectional pattern.

In addition to cohort and age effects, patterns of rates can be influenced by the *so-called "period effect." The term period effect is frequently used to refer to a global* shift or change in trends that affect the rates across birth cohorts and age groups (Exhibit 1-1). Any phenomenon occurring at a specific point in time (or during a specific period) that affects an entire population (or a significant segment of it), such as a war, a new treatment, or massive migration, can produce this change independently of age and birth cohort effects. A hypothetical example is shown in Figure 1-5. This figure shows data similar to those used in the previous example (Figure 1-3), except that in this case the rates level off in 1995 for all cohorts (i.e., when the 1970 cohort is 25 years old on the average, when the 1960 cohort is 35 years old, and so on).

Period effects on prevalence rates can occur, for example, when new medications or preventive interventions are introduced for diseases that previously had poor prognoses, as in the case of the introduction of insulin, antibiotics, and the polio vaccine.

It is important to understand that the so-called birth cohort effects may have little to do with the circumstances surrounding the time of birth of a given cohort of individuals. Rather, cohort effects may result from the lifetime experience (including, but not limited to, those surrounding birth) of the individuals born at a given point in time that influence the disease or outcome of interest. For example, currently observed patterns of association between age and coronary heart disease (CHD) may have resulted from cohort effects related to changes in diet (e.g., fat intake) or smoking habits of adolescent and young adults over time. It is well known that coronary atherosclerotic markers,

**FIGURE 1-5** Hypothetical example of period effect: an event happened in 1995 that affected all birth cohorts (1930–1970) in a similar way and slowed down the rate of increase with age. The solid line represents the observed cross-sectional age pattern in 2005.

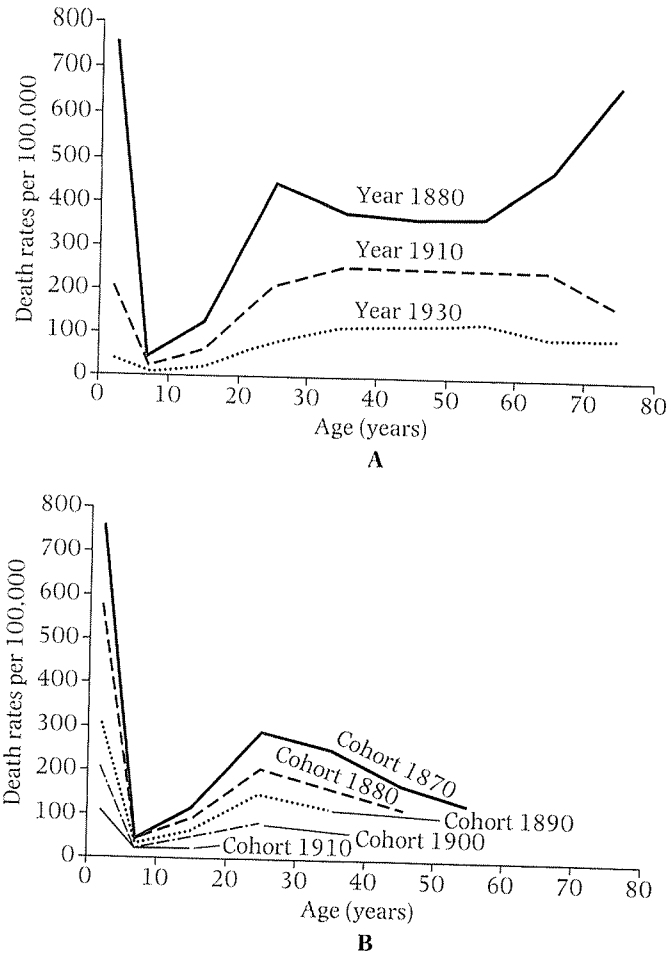



such as thickening of the arterial intima, frequently develop early in life.[4] In middle and older ages, some of these early intimal changes may evolve into raised atherosclerotic lesions, eventually leading to thrombosis, lumen occlusion, and the resulting clinically manifest acute ischemic events. Thus, a young adult's dietary and/or smoking habits may influence atherosclerosis development and subsequent coronary risk. If changes in these habits occur in the population over time, successive birth cohorts will be subjected to changing degrees of exposure to early atherogenic factors, which will determine in part future cross-sectional patterns of the association of age with CHD.

Another way to understand the concept of cohort effects is as the result of an *interaction* between age and calendar time. The concept of interaction is discussed in detail in Chapter 6 of this book. In simple terms, it means that a given variable (e.g., calendar time in the case of a cohort effect) *modifies* the strength or the nature of an association between another variable (e.g., age) and an outcome (e.g., coronary atherosclerosis). In the previous example, it means that the way age relates to the development of atherosclerosis changes over time as a result of changes in the population prevalence of key risk factors (e.g., dietary/smoking habits of young adults). In other words, calendar time-related changes in risk factors *modify* the association between age and atherosclerosis.

Cohort–age–period analyses can be applied not only to prevalence data but also to incidence and mortality data. A classic example is Wade Hampton Frost's study of age patterns of tuberculosis mortality.[5] Figure 1-6 presents two graphs from Frost's landmark paper. With regard to Figure 1-6A, Frost[5(p.94)] noted that "looking at the 1930 curve, the impression given is that nowadays an individual encounters his greatest risk of death from tuberculosis between the ages of 50 and 60. But this is not really so; the people making up the 1930 age group 30 to 60 have, in earlier life, passed through *greater* mortality risk" (emphasis in original). This is demonstrated in Figure 1-6B, aptly used by Frost to show how the risk of tuberculosis death after the

**FIGURE 1-6** Frost's analysis of age in relation to tuberculosis mortality (males only). (A) Massachusetts death rates from tuberculosis, by age, 1880, 1910, 1930. (B) Massachusetts death rates from tuberculosis, by age, in successive 10-year cohorts.

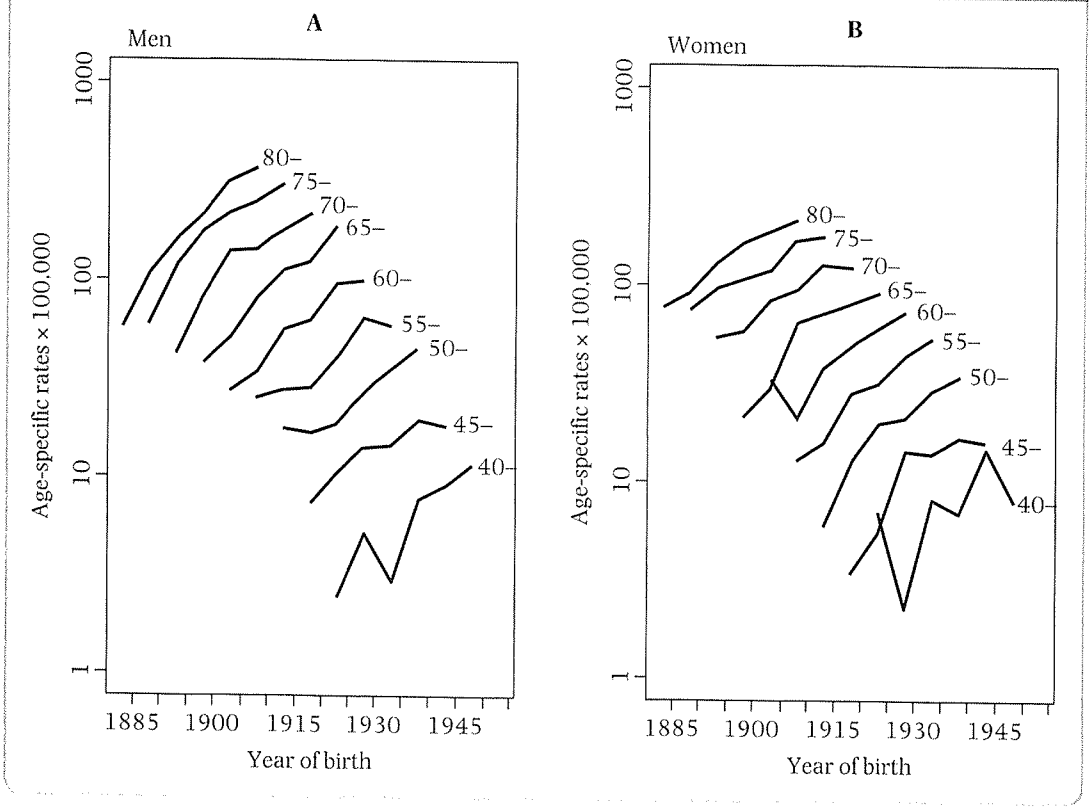



*Source:* Reprinted with permission from WH Frost. The Age-Selection of Tuberculosis Mortality in Successive Decades. *American Journal of Hygiene*, Vol 30, pp. 91–96, © 1939.

first few years of life is actually highest at ages 20 to 30 years for cohorts born in 1870 through 1890.

Another, more recent, example is shown in Figure 1-7, based on an analysis of age, cohort, and period effects on the incidence of colorectal cancer in a region of Spain.[6] In these figures, birth cohorts are placed on the $x$ axis (as in Figure 1-4). These figures show strong cohort effects: for each age group, the incidence rates of colorectal cancer tend to increase from older to more recent birth cohorts. An age effect is also evident, as for each birth cohort (for any given year-of-birth value in the horizontal axis) the rates are higher for older than for younger individuals. Note that a logarithmic scale was used in the ordinate in this figure, in part because of the wide range of rates needed to be plotted. (For further discussion of the use of logarithmic vs arithmetic scales, see Chapter 9, Section 9.3.5.)

**FIGURE 1-7** Trends in age-specific incidence rates of colorectal cancer in Navarra and Zaragoza (Spain). The number next to each line represents the initial year of the corresponding 5-year age group.



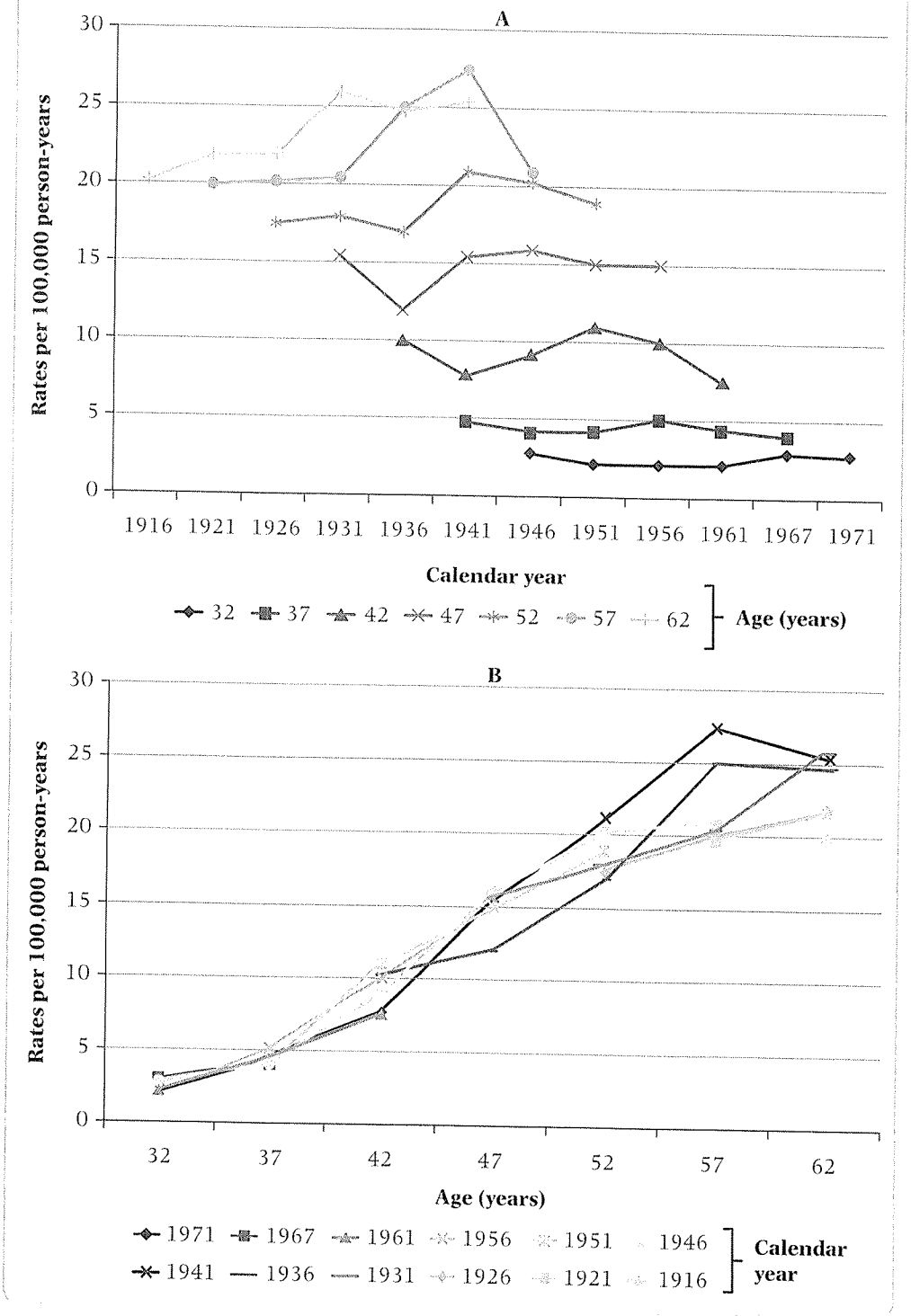

*Source:* Reprinted with permission from G. López-Abente et al., Age-Period-Cohort Modeling of Colorectal Cancer Incidence and Mortality in Spain. *Cancer Epidemiology, Biomarkers, and Prevention*, Vol 6, pp. 999–1005. © 1997.

An additional example of age and birth cohort analysis of incidence data is shown in Figure 1-8. This figure shows the incidence of ovarian cancer in Mumbai, India, by age and year of birth cohort.[7] This is an example in which there is a strong age effect, particularly for the cohorts born from 1940 through 1970—that is, rates increase dramatically with age through age 52 years—but virtually no cohort effect, as indicated by the approximate flat pattern for the successive birth cohorts for each age group (the figure shows the midpoint of each age group). It should be manifest that, with very little cohort effect, the same age patterns for rates are found in cross-sectional and cohort curves (Figure 1-8B).

Period effects associated with incidence rates tend to be more prominent for diseases for which the cumulative effects of previous exposures are relatively unimportant, such as infectious diseases and injuries. Conversely, in chronic diseases such as cancer and cardiovascular disease, cumulative effects are usually important, and thus, cohort effects tend to affect incidence rates to a greater extent than period effects.

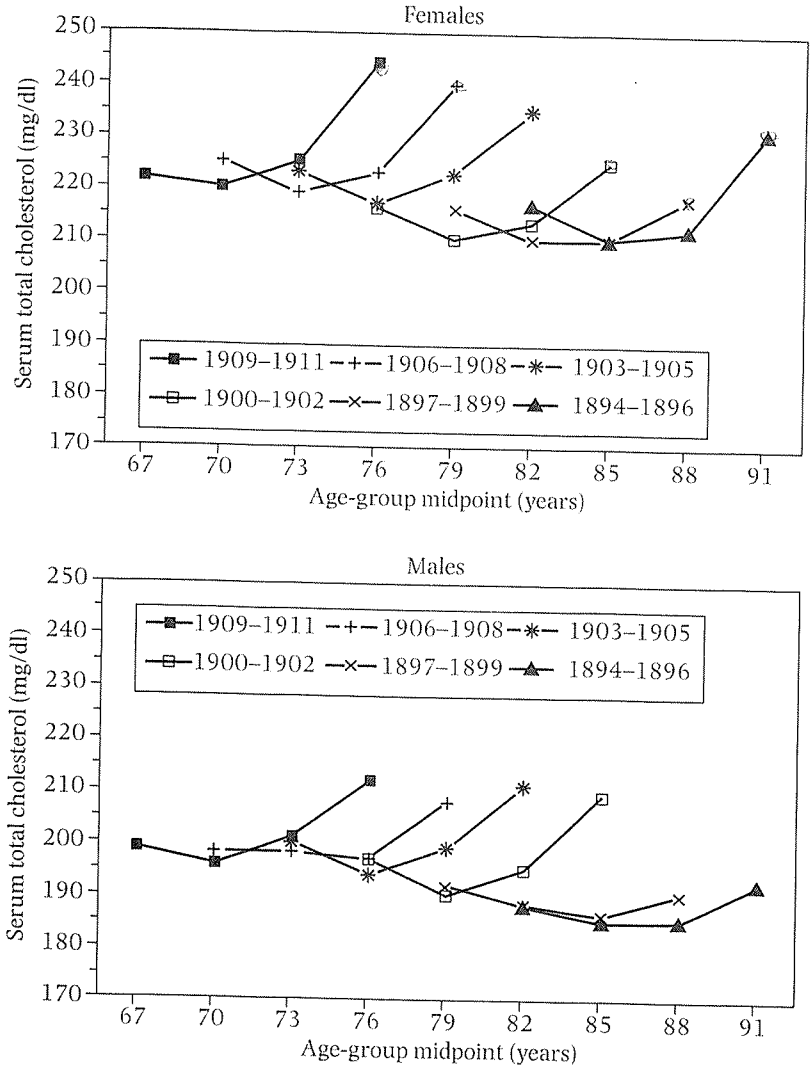
These methods can also be used to study variables other than disease rates. An example is the analysis of age-related changes in serum cholesterol levels shown in Figure 1-9, based on data from the Florida Geriatric Research Program, an ongoing program designed to provide free medical screening for older people.[8] This figure reveals a slight cohort effect, in that serum cholesterol levels tend to be lower in older than in more

**FIGURE 1-8** Incidence rates of ovarian cancer per 100,000 person-years, by birth cohort (A) and by age (B).




*Source:* Adapted from PK Dhillon et al., Trends in Breast, Ovarian and Cervical Cancer Incidence in Mumbai, India Over a 30-Year Period, 1976–2005: An Age-Period-Cohort Analysis. *British Journal of Cancer*, Vol 105, No 5, pp. 723–730, © 2011.

**FIGURE 1-9** Sex-specific mean serum cholesterol levels by age and birth cohort: longitudinal data from the Florida Geriatric Research Program, Dunedin County, Florida, 1976 to 1987.




*Source:* Reprinted with permission from CJ Newschaffer, TL Bush, and WE Hale. Aging and Total Cholesterol Levels: Cohort, Period, and Survivorship Effects. *American Journal of Epidemiology*. Vol 136, pp. 23–34, © 1992.

recent birth cohorts for most age groups. A J- or U-shaped age pattern is also seen; that is, for each birth cohort, serum cholesterol tends to first decrease or remain stable with increasing age and then increase to achieve its maximum value in the oldest members of the cohort. Although at first glance this pattern might be considered an "age effect," for each cohort the maximum cholesterol values in the oldest age group coincide with a single point in calendar time: 1985 through 1987 (i.e., for the 1909–1911 birth cohort at 76 years of age, for the 1906–1908 cohort at 79 years of age, and so on), leading Newschaffer et al. to observe that "a period effect is suggested by a consistent change in curve height at a given time point over all cohorts. . . . Therefore, based on simple

visual inspection of the curves, it is not possible to attribute the consistent U-shaped increase in cholesterol to aging, since some of this shape may be accounted for by period effects."[8(p.26)]

In complex situations, it may be difficult to clearly differentiate age, cohort, and period effects. In these situations, such as that illustrated in the preceding discussion, multiple regression techniques can be used to disentangle these effects. Describing these techniques in detail is beyond the scope of this book. (A general discussion of multiple regression methods is presented in Chapter 7, Section 7.4.) The interested reader can find examples and further references in the original papers from the previously cited examples (e.g., López-Abente et al.[6] and Newschaffer et al.[8]).

Finally, it should be emphasized that birth cohort effects may affect associations between disease outcomes and variables other than age. Consider, for example, a case-control study (see Section 1.4.2) in which cases and controls are closely matched by age (see Section 1.4.5). Assume that, in this study, cases are identified over a 10-year span (e.g., from 1960 through 1969) and controls at the end of the accrual of cases. In this study, age *per se* does not act as a confounder, as cases and controls are matched on age (see Section 5.2.2); however, the fact that cases and controls are identified from different birth cohorts may affect the assessment of variables, such as educational level, that may have changed rapidly across birth cohorts. In this case, birth cohort, but not age, would confound the association between education and the disease of interest.

## 1.3 ECOLOGIC STUDIES

The units of observation in an ecologic study are usually geographically defined populations (such as countries or regions within a country) or the same geographically defined population at different points in time. Mean values* for both a given postulated risk factor and the outcome of interest are obtained for each observation unit for comparison purposes. Typically, the analysis of ecologic data involves plotting the risk factor and outcome values for all observation units to assess whether a relationship is evident. For example, Figure 1-10 displays the death rates for CHD in men from 16 cohorts included in the Seven Countries Study plotted against the corresponding estimates of mean fat intake (percent calories from fat).[9] A positive relationship between these two variables is suggested by these data, as there is a tendency for the death rates to be higher in countries having higher average saturated fat intakes.

Different types of variables can be used in ecologic studies,[10] which are briefly summarized as follows:

- *Aggregate measures* that summarize the characteristics of individuals within a group as the mean value of a certain parameter or the proportion of the population or group of interest with a certain characteristic. Examples include the prevalence of a given disease, average amount of fat intake (Figure 1-10), proportion of smokers, and median income.
- *Environmental measures* that represent physical characteristics of the geographic location for the group of interest. Individuals within the group may have different degrees of exposure to a given characteristic, which could theoretically be measured. Examples include air pollution intensity and hours of sunlight.

*A mean value can be calculated for both continuous and discrete (e.g., binary) variables. A proportion is a mean of individual binary values (e.g., 1 for presence of a certain characteristic, 0 if the characteristic is absent).