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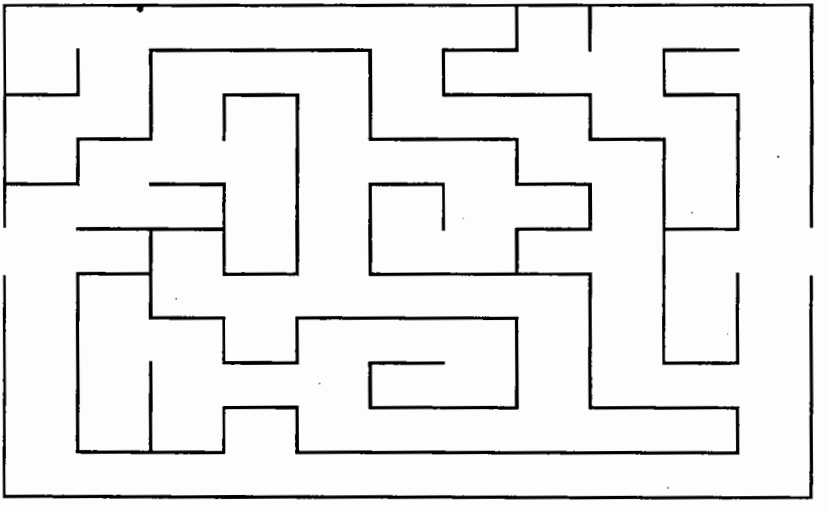
Cohort Studies



A population of known size, an elapse of time, the dates of onset: these are the necessary elements for quantifying the rate of occurrence of disease. In *closed cohort studies*, study subjects are observed continuously from the time of joining the study forward. "Exposure" is a state or characteristic present at the outset, and disease occurrences are accumulated to the end of follow-up. In *open cohort studies* there remains the key element of comparison of attained states (of exposure or of life style, for example), but the onset of the relevant state may lie outside the period of observation. *Case-control studies*, a special class of cohort studies in which the source population is studied on a sample basis, will be treated in the next chapter.

Closed Cohort Studies

Consider an example from infectious disease epidemiology.

Example 5.1. *Foodborne streptococcal pharyngitis.*[45]

During June 21-24, 1979, 300 Greek-Americans held a convention in Palm Beach. There was an outbreak of pharyngitis during the convention. Fearing Legionnaire's Disease, local officials called on the United States Centers for Disease Control (CDC). Through interviews and mailed questionnaires, a CDC team attempted to identify the foods eaten and events attended by every conventioneer, and to define the time of onset of symptoms of pharyngitis. Cases of "convention-associated" pharyngitis were defined as any sore throat in a conventioneer that developed after arrival at the convention but before June 29. Because the study took place after the convention was over, it was possible to obtain throat cultures only from those conventioneers whose homes were near Palm Beach. Cultures were taken from both symptomatic and asymptomatic subjects, and cases in which there was a positive culture for Lancefield group G streptococci were classed as "culture-confirmed."

Populations at risk among the conventioneers were defined according to activities undertaken, and the risk of developing pharyngitis was calculated for each population defined by participation in a particular activity. After some preliminary review of the data, the investigators focused their attention on two events: a luncheon on June 22 and a dance held that same evening. It was possible to classify 226 people according to their attendance at the luncheon and the dance, and according to their later pharyngitis, as shown in Table 5.1.

Two of eight waiters and one of five cooks for the luncheon also developed pharyngitis. On the evening before the luncheon the cook who became ill had prepared a chicken salad consumed by essentially all those who partook of the meal. She later had a throat culture positive for group G streptococcus. Of 20 throat culture isolates of beta-hemolytic streptococci obtained by the CDC from symptomatic conventioneers, 17 were group G. The CDC investigators concluded that there had been an outbreak of foodborne group G streptococcal pharyngitis, probably with the

45. Stryker WS, Fraser CW, Facklam RR. Foodborne outbreak of group G streptococcal pharyngitis. Am J Epidemiol 1982;116:533-40

Table 5.1 Cumulative incidence of pharyngitis in relation to attendance at the luncheon and the dance

Luncheon	Dance	Number	Cases	Percent ill
No	No	40	1	3 %
No	Yes	77	11	14 %
Yes	No	23	8	35 %
Yes	Yes	86	47	55 %

chicken salad as the common vehicle of exposure. They did not feel that they had a satisfactory explanation for the apparent association of disease with attendance at the dance.

This example differs little in form from problems that might be encountered in the study of cancer, AIDS, or myocardial infarction. Researchers who work with infectious diseases have access to prior bacteriologic knowledge that enables them to focus their inquiry, but the questions they encounter are very much like those that appear in cohort studies of all kinds.

Definition of populations at risk. The population targeted for investigation consisted of a fully enumerated group of individuals (persons who attended the convention), whose experience was under study for an explicit period of time (June 21 to 29, 1979). Subcohorts for comparison were defined by having achieved some state (the states of having attended the luncheon or the dance), and for those subcohorts the study began as of the time they achieved the states (after the dance on June 22). Note that the state defining the cohorts is not exposure to group G streptococcus, which is not known or even knowable for the entire population; the defining state is rather participation in an activity, such as attendance at the dance or luncheon; the activity is a correlate of the suspected source of disease.

The persons studied did not consist of all those who attended the convention, but rather those for whom it was possible to obtain data. (Table 5.1 accounts for only 75 percent of the conventioneers.) If a person's willingness to participate in this study were affected by whether or not he developed a sore throat, the apparent overall attack rates would be distorted. If willingness to participate depended on both sore throat and attendance at the dance or the luncheon (as

might be the case if conventioneers had specific hypotheses about the origin of their illness), then the relations between events attended and disease could be distorted as well.

Definition of disease outcomes. "Convention-associated" pharyngitis was given an operational definition for the purposes of epidemiologic study; it was not the idealized (and observable) event causally linked to a particular bacterial exposure at the convention. A few cases actually due to the contamination of the chicken salad may not have been manifest by June 29; almost certainly, some of the cases that appeared after June 22 and before June 29 had no link with any of the events at the convention. In the absence of a way to distinguish those cases that were part of the epidemic from those that were coincidental, the CDC group invoked a temporal criterion whose purpose was to include as many of the truly epidemic cases and as few of the background cases as possible.

Time definitions of case eligibility and of cohort observation are logically interchangeable. If they are not identical, then there is a contradiction implicit in the study design. The specification of the population at risk immediately defines in part the eligible cases: they must have been members of the population when they became ill. In an analogous manner, disease definition carries an implicit definition of the population at risk. Thus the choice of June 29 as the last allowable day for the onset of a "convention-associated" pharyngitis delimited the effective period of observation of the cohorts.

In the same way that temporal definitions of disease status and cohort membership must be congruent, so must other aspects of case definition. The entity actually recorded in Table 5.1 is "sore throat"; attribution of the epidemic to group G streptococcal disease is the result of intensive study of a nonrandom subsample of the population. Had the CDC investigators insisted on culture-proven streptococcal infection as a defining characteristic of a case, they would have in effect reduced the cohorts under study to those in whom a throat culture was taken. Since persons not cultured could not possibly have been termed cases (no matter what their actual disease experience), then they would not have been members of the cohort under study.

Restriction of eligible cases to those with culture-proven disease would have led to a tractable problem of cohort definition in this example because there is little ambiguity as to who was given an opportunity for diagnosis. The situation may be less clear in investigations of chronic diseases that might be diagnosed only through procedures that are not in widespread use. For example, if one were to insist on a full autopsy for case definition in a study of cancer, then the population under investigation would really consist of all those persons in the cohort who would have had an autopsy, had they died with cancer. Ascertaining cohort membership on the basis of a condition that is not manifest is logically acceptable, but poses practical problems. In effect we are left to study not the occurrence of disease, but the occurrence of disease-plus-diagnosis. If exposure is a determinant of the performance of necessary diagnostic procedures, then exposure will be a determinant of diagnosed disease, even if it bears no causal relation to disease itself.

Correct diagnosis of disease is crucial to epidemiologic study, yet it appears that in some cases the determinants of diagnostic procedures may masquerade as determinants of disease. This happens when a "definitive" diagnostic maneuver is rarely performed. In such circumstances the epidemiologic definition of disease must be refocussed on ascertainable outcomes such as "sore throat," "sudden death," or "wasting and diarrhea." The relation between these observables and the diseases that they might be taken to represent, group G pharyngitis, ventricular fibrillation, or AIDS, respectively may need to be the object of a separate investigation if the connection is at all in doubt. When diagnostic opportunity is very widespread, the benefits conferred by the use of a rigorous case definition most often outweigh the distortion introduced by selective access.

Open Cohort Studies

In the preceding example, there were two elements of the study which were assumed to have a simple structure: a single disease risk was to be estimated for each exposure, and the populations under study were taken to be closed as to membership. Neither simplicity of the relation of risk to time, nor the integrity of populations under study carries over to studies of most chronic diseases, in which the pace of time is measured in years rather than days.

Because time affects risks and changes people, the unit of observation in studies of chronic disease shifts away from the individual and toward a quantum of experience that incorporates both individual identity and the passage of time. An individual's person time is measured by the length of time during which that individual resides in a (more or less) homogeneous state of risk, and is characterized according to categories derived from the subject's prior history. The typical unit of person time in cancer epidemiology is the "person year"; in the study of vaccine reactions it might be the "person day." The time units are interconvertible: one person year equals 365.25 person days. The usual convention for recording person time is to select the largest time unit over which changes in the risk under study are negligibly small.

Collection and categorization of data in studies of person time. For each homogeneous period of risk in a study subject's life, the researcher notes the duration and adds that amount of person time to a category based on the individual's past and current experience. Since an individual's past evolves with time, his life experience may contribute sequentially to many categories of person time. He ages, he suffers new exposures, he accumulates perhaps larger and larger amounts of past exposures. Each new category of experience is segregated and its duration added to the summed durations of experience of other people in similar circumstances.

The investigator accumulates a table of person years experienced by study subjects, cross-classified by the factors (such as age, sex, exposure, and calendar year) considered relevant to the occurrence of disease. At the same time, the investigator builds a parallel table of counts of events (disease onsets) under study; each event is assigned to a cell in the table of events that corresponds to the exact category of person time within which the event took place.

Ideally, the categories tabulated represent pools of human experience that are homogeneous insofar as the expected incidence rate of disease is concerned. Most incidence rates evolve continuously over time, however, and no system of cut-points to distinguish categories is entirely satisfactory. The conventions most often used represent a balance between conflicting demands of detail in the description of risk (which would require many narrowly defined categories) and precision in each of the category-specific estimates (which may require many person years of experience in each category and therefore lead to more encompassing boundaries). Typical cut-points in chronic disease studies are five-year groups of age, of

duration of exposure, of time since exposure, or of calendar year of observation. No "typical" convention should be adopted, however, unless the investigator is satisfied that the expectation of a nearly homogeneous incidence rate within each category is approximately correct.

The following example illustrates the construction of the data for a cohort study of cancer mortality.

Example 5.2. *Lung cancer in asbestos workers.*[46]

For a study of the effects of asbestos exposure, some 17,800 members of the Union of Heat and Frost Insulation Workers were registered on January 2, 1967, with information obtained on their dates of birth and entry into the union. This latter date was taken as the date of first exposure to large quantities of asbestos-containing products. All deaths in union members (active or retired) were reported through the union to researchers, who sought both the death certificates and all available medical data on each of the decedents in order to characterize the cause of death. The number of man years of observation in five-year categories of time since first exposure and of age were tabulated for the full membership, and each death was assigned to that category to which the union member was contributing person time of experience at the time of his death.

Table 5.2 presents an extract of the information acquired through this study in the course of the first ten years of data collection. For each time interval listed in the first column, the second column shows the number of men who contributed some amount of person time to that category. In the third column, the sums of the individual contributions to person time in each category are listed, and in the next column are the numbers of deaths from lung cancer observed in each category. The last column gives the lung cancer mortality rate per 1000 person years, obtained by dividing the number of deaths from lung cancer in each category by the accumulated person years (measured in thousands) for the same category.

46. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 1980;46:2736-40.

Table 5.2 Lung cancer mortality and time since onset of exposure to asbestos

Time since first exposure (years)	Number of men who contributed experience	Person years of experience	Deaths from lung cancer	Deaths per 1000 person years
15 - 19	9948	34,066	27	0.79
20 - 24	8887	31,268	57	1.82
25 - 29	6596	20,657	96	4.64
30 - 34	3547	11,598	103	8.88
35 - 39	2020	5,403	57	10.55
40 - 44	1108	3,160	31	9.81

Several features of Table 5.2 underscore the point that person time, not persons, is the object of classification and study. (1) The sum of the second column exceeds the total number of men observed in the study, because most men contributed to more than one category of time since first exposure. (2) Men who died of lung cancer contributed person time of experience both to the category that they were in when they died and to any previous category during which they had been observed. The person time at risk in a cohort study is contributed by those who later suffer an event as well as by those who never do. (3) Comparisons between any pair of mortality rates in Table 5.2 may involve the experience of some individuals who contribute to both exposure categories. By contrast, all comparisons in Table 5.1 necessarily involved separate individuals.

The mortality rates listed in the last column of Table 5.2 are examples of the fundamental epidemiologic measure offered by an open cohort study. From the pattern of mortality rates shown, it is evident that the lung cancer mortality rate rose dramatically with the passage of time from first exposure to asbestos, and that there was a plateau beginning after some 35 years. A deceleration in the rise of lung cancer rates after many years appears to be a nearly constant

feature of cohorts of asbestos workers followed for the long term.[47] The relative mortality rates, as compared to the rates in the general population, actually tend to decline.

47. Walker AM. Declining relative risks for lung cancer after cessation of asbestos exposure. J Occup Med 1984;26:422-6