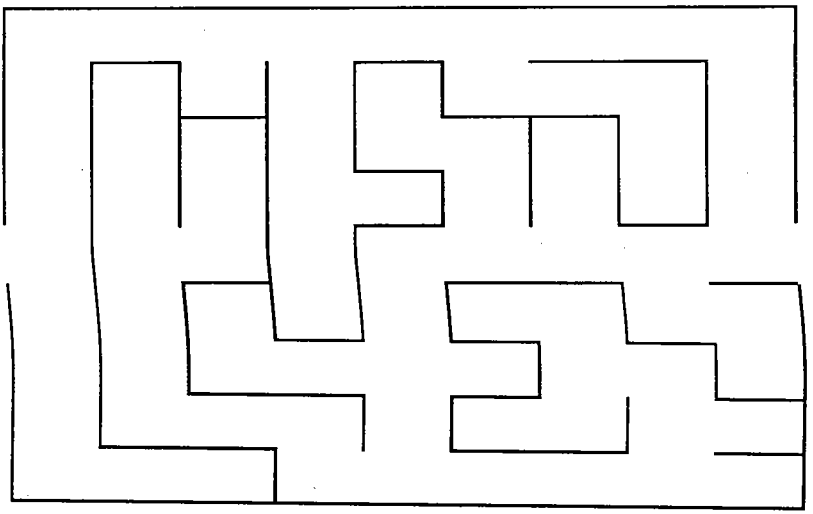
8

Estimation



On the basis of data, we make estimates. The estimates are constructed in such a way that they bear a known relation to the parameters of processes that gave rise to the data. This chapter describes the mechanics of obtaining estimates and of judging the relation between estimate and parameter for closed and open cohort studies, and for case-control studies. All the statistical terms used here are defined in Chapter 13.

Analysis of Closed Cohort Studies

The methods presented here will be illustrated using the data of Example 5.1, which you should review before continuing.

Calculation of attack rates and cumulative incidence differences. Since pharyngitis could only occur once during the period of observation, the designation of each of the cohort members as a case or non-case was unambiguous, and it was reasonable to calculate the fraction of persons in each cohort who became ill. This is the cumulative incidence, as defined in Chapter 1. Infectious disease epidemiology has its own term for the cumulative incidence: *attack rate* (*AR*).[55]

Attack rate. *The attack rate is the cumulative incidence of disease in persons who are exposed to an agent whose effect is shorter than the time of potential follow-up. The period of follow-up begins at the time of exposure and continues over a closed interval that allows the expression of all possible new cases attributable to the exposure.*

The attack rate provides an estimate of the probability of infection that each of the cohort members faced at the beginning of the convention. Since the attack rate and the cumulative incidence are identical quantities, the latter term will be used in the remainder of this section for consistency. Readers should bear in mind that the infectious disease literature uses the former term. The cumulative incidence difference is obtained by subtracting the cumulative incidence in an unexposed group from that in an exposed group. Thus, in Table 5.1, the cumulative incidence difference associated with luncheon attendance is (47/86)-(11/77) or 40.4 percent in those who attended the dance and (8/23)-(1/40) or 32.3 percent in those who did not attend the dance.

Cumulative incidences and cumulative incidence differences observed in particular studies are estimates. Approximate confidence intervals for each of the corresponding probabilities and for their differences can be derived by assuming that the number of cases is distributed as a binomial variable.

55. The word "rate" in this term is a misnomer in the system of nomenclature presented here, since the attack rate is not a rate but a proportion.

Binomial distribution *is the probability distribution that describes the number of events observed in N opportunities to observe an event, when the probability of observing a single event at any opportunity is π, and is unaffected by the observation of an event at any other opportunity.*

$$\Pr(x \mid N) = \frac{N!}{x!(N-x)!}\pi^x(1-\pi)^{N-x}$$

$$E(X) = \pi N$$

$$\mathrm{Var}(X) = N\pi(1-\pi)$$

The range of possible values for x is [0,N]. π is the binomial parameter.

In this definition, as elsewhere, "Pr($x|N$)" means "the probability of observing x cases among N observed persons"; "E(X)" means "the expected value of the random variable X"; and "Var(X)" means "the variance of the random variable X."

In the calculation of a cumulative incidence, x is the number of cases and N is the number of individuals in the population at risk; the cumulative incidence is given by x/N. The variance of x/N is $x(N-x)/N^3$.[56] The bounds of an approximate 95 percent confidence interval for the probability of pharyngitis, of which x/N is an estimate, are obtained by adding and subtracting 1.96 times the standard error (the square root of the variance) to and from x/N. For those who attended the luncheon and the dance, x is 47 and N is 86, so that

$$CI = AR = x/N = 47/86 = 0.547$$

The 95 percent confidence bounds for the probability of pharyngitis are

56. c.f. Table 1.2 and Chapter 13. Note that

$$CI = \frac{x}{N}$$

$$\frac{CI(1-CI)}{N} = \frac{x(N-x)}{N^3}$$

$$\text{lower} = \frac{x}{N} - 1.96\sqrt{\frac{x(N-x)}{N^3}}$$

$$= \frac{47}{86} - 1.96\sqrt{\frac{47(86-47)}{86^3}}$$

$$= 0.441$$

$$\text{upper} = \frac{x}{N} + 1.96\sqrt{\frac{x(N-x)}{N^3}}$$

$$= \frac{47}{86} + 1.96\sqrt{\frac{47(86-47)}{86^3}}$$

$$= 0.652$$

The cumulative incidence for conventioneers who attended both the luncheon and the dance was 55 percent, with 95 percent confidence bounds of 44 and 65 percent. (In the above calculation, an extra digit has been retained in the values derived in intermediate steps for accuracy. In practice, all intermediate values should be retained with as many digits as possible, with rounding employed only for the final result.)

The calculation of the confidence interval above has two important limitations. First, the method employed is a *large sample* technique, whose accuracy improves as the number of study subjects becomes larger. When the smallest count involved in the calculation is larger than 30, then the results are virtually identical to more accurate methods of calculation, which can be found in intermediate textbooks of epidemiology or statistics. When the smallest count is ten or greater, the results are close enough for most any purpose; when the smallest count is five or less, the method gives bounds that are only roughly indicative of the range of parameter values.

The second important feature is that the method assumes independence of individual results. The risk in any individual is assumed not to be affected by the outcome in other individuals. In contemporary epidemiology, this means that the method given is inappropriate when the number of ill persons is the result of person-to-person transmission of risk.

The variance of the cumulative incidence difference can be estimated by summing the estimated variances of the cumulative incidences that make up the cumulative incidence difference. (See Chapter 13 for rules about the manipulation of variances.) An estimate of the variance associated with the cumulative incidence difference between the dancers attending the luncheon and those not doing so is

$$\text{Var}(CID) \doteq \frac{47(86-47)}{86^3} + \frac{11(77-11)}{77^3}$$

$$= 0.004472$$

Thus

$$CID = \frac{47}{86} - \frac{11}{77}$$

$$= 0.4037$$

and the 95 percent confidence bounds for the difference in the probabilities of pharyngitis are

$$\text{lower} = 0.4037 - 1.96\sqrt{0.004472}$$

$$= 0.273$$

$$\text{upper} = 0.4037 + 1.96\sqrt{0.004472}$$

$$= 0.535$$

Summarizing experience across several strata. The cumulative incidence differences associated with attending the luncheon in those who attended the dance and in those who did not attend the dance are somewhat different (40.4 percent and 32.3 percent, respectively). There are a variety of ways in which these two estimates might be summarized in a single overall figure. One approach is to take a weighted average of dancers' and nondancers' cumulative incidences among the luncheon attendees, and then to do the same for the nonattendees, using the same weights. The weighted averages are said to be *adjusted* for the effects of attendance at the dance. Because the same weighting scheme is used to adjust the rates of the luncheon "exposed" and "unexposed" groups, the comparison between exposure groups is a valid one. The resulting weighted averages are referred to as *standardized* cumulative incidences.

Standardization. *Standardized measures are formed from a series of individual measures by taking a weighted average of the individual values.*

Standard. *The set of weights used for standardization is the standard. These weights sum to 1.*

One convenient standard is the distribution of dancers among luncheon attendees. Of the attendees, 86/(86+23) or 78.9 percent went to the dance, and 23/(86+23), or 21.1 percent, did not. Call the cumulative incidences that are standardized over categories of dance attendance the *standardized cumulative incidences* (*SCI*). The cumulative incidences for dancers and nondancers among luncheon attendees were 47/86 (54.7 percent) and 8/23 (34.8 percent), respectively. The *SCI* for luncheon attendees is

$$SCI(\text{exposed}) = \left(\frac{86}{86+23}\right)\left(\frac{47}{86}\right) + \left(\frac{23}{86+23}\right)\left(\frac{8}{23}\right)$$

$$= 0.5046$$

For those who did not attend the luncheon, the cumulative incidences among dancers and nondancers were 11/77 (14.3 percent) and 1/40 (2.5 percent), respectively. The *SCI* for nonattendees is

$$SCI(\text{unexposed}) = \left(\frac{86}{86+23}\right)\left(\frac{11}{77}\right) + \left(\frac{23}{86+23}\right)\left(\frac{1}{40}\right)$$

$$= 0.1180$$

The standardized cumulative incidence difference (*SCID*) is the difference between the standardized cumulative incidences.

$$SCID = SCI(\text{exposed}) - SCI(\text{unexposed})$$

$$= 0.3866$$

Note that this result is identical to the result that would be obtained by applying the standard weights to the stratum-specific cumulative incidence differences. The cumulative incidence differences are 0.4037 for those who attended the dance and (8/23)-(1/40) = 0.3228 for those who did not. Standardized over categories of dance attendance, the cumulative incidence difference would be

$$SCID = \left(\frac{86}{86+23}\right)(0.4037) + \left(\frac{23}{86+23}\right)(0.3228)$$

$$= 0.3866$$

The standardized cumulative incidence difference can be seen as a weighted average of the component cumulative incidence differences.

The variance of a weighted average is given by the sum of the component variances, each weighted by the square of the corresponding weight, so that

$$\text{Var}(SCID) = \left(\frac{86}{86+23}\right)^2(0.004472) + \left(\frac{23}{86+23}\right)^2(0.01047)$$

$$= 0.003250$$

95 percent confidence bounds to the *SCID* are therefore

$$\text{lower} = 0.3866 - 1.96\sqrt{0.003250}$$

$$= 0.2749$$

$$\text{upper} = 0.3866 + 1.96\sqrt{0.003250}$$

$$= 0.4983$$

The luncheon "effect" is standardized according to the dancing choices of those who actually attended the lunch. The final measure is intuitively satisfying in that it is directly tied to the experience of the exposed group: it addresses the question "What would have been the difference between those who attended the luncheon and those who did not if the nonattendees had the same fraction of dancers as those who attended?" Other weighting schemes that might have been used include an external standard (such as equal weights for each group), or an internal standard based on the reciprocals of the variances[57] of the stratum-specific cumulative incidence differences. This last standard minimizes the variance of the final

57. The reciprocal of the variance of an estimate is also known as the "information" contained in the estimate. Very precise estimates have small variance and high information.

estimate, but its proper use presupposes that the only source of discrepancy between the stratum-specific cumulative incidence differences is chance.

Confounding. If the interest in Table 5.1 had focussed on the cumulative incidence difference associated with attendance at the dance, the investigators could have calculated estimates of (47/86) - (8/23) or 20 percent in those who attended the luncheon and (11/77) - (1/40) or 12 percent in those who did not. Any standardized estimate of an overall effect would lie between these two values. If luncheon attendance were ignored, a crude cumulative incidence difference might also have been calculated as

$$CID = \frac{47+11}{86+77} - \frac{8+1}{23+40}$$

$$= 0.213$$

or 21 percent. This value lies outside of the range of stratum-specific estimates. Because luncheon attendance was more common among dancers than among those who did not dance, the crude cumulative incidence difference reflects a part of the cumulative incidence associated with luncheon attendance, in addition to the effect of dance attendance on risk. The crude cumulative incidence difference therefore provides a biased estimate of the increase in probability of pharyngitis associated with attendance at the dance.

Analysis of Open Cohort Studies

Example 5.2 will be used to illustrate the techniques presented here.

Error estimates and comparisons of incidence rates. Just as the observed proportion of the disease in a closed cohort study is an estimate of the underlying probability of developing disease, so the ratio of cases to person time, the incidence rate, provides an estimate of the underlying hazard of disease. The most straightforward technique for assessing the variability of incidence rates in open cohort studies is based on a treatment of the incidence rate calculation as if the numerator (the number of cases) were variable and the denominator (the amount of person time) were fixed. If x is the number of observed events and P is the person time at risk, then x is the realization of what is called a Poisson process. The probability distribution from which x is drawn is the Poisson distribution.[58]

Poisson distribution *is the probability distribution that describes the number of events observed in a block of person time when the expected number of events is directly proportional to the total person time of observation. Let θ be the expected number of events per unit of person time and $\lambda = \theta P$ be the number of events expected in a block of person time of size P.*

$$\Pr(x) = \frac{\lambda^x e^{-\lambda}}{x!}$$

$$E(X) = \lambda$$

$$\mathrm{Var}(X) = \lambda$$

The range of possible values for x is $[0, \infty)$. λ is the Poisson parameter. If P is imagined as being composed of a very large number of discrete units of person time, so that the probability of an event in any person time unit is very small, then the probability distribution of the number of events in P may also be considered to be binomial, with N taken as the number of discrete person time units. All the formulas above are derivable from their binomial counterparts in the limiting case in which N approaches infinity, with P and λ constant.

The number of observed events x is an estimate of a Poisson parameter λ. The incidence rate estimate IR is given by x/P, with variance x/P^2.[59] The mortality rate estimate and its variance for the period from 30 through 34 years since first exposure (Table 5.2) are given by

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58. The development here presumes that the expected number of cases is directly proportional to the amount of person time of observation. Put another way, we presume that there is no element of contagion, in which the probability of a case occurring is a function of the number of other cases that have occurred.

59. c.f. Table 1.2 and Chapter 13. Note that

$$IR = \frac{x}{P}$$

$$\frac{IR}{P} = \frac{x}{P^2}$$

$$IR = \frac{103}{11,598}$$

$$= 0.008881 \text{ cases per person year}$$

$$\text{Var}(IR) = \frac{103}{(11,598)^2}$$

$$= 7.657 \times 10^{-7}$$

The 95 percent confidence bounds are

$$\text{lower} = 0.00881 - 1.96\sqrt{7.657 \times 10^{-7}}$$

$$= 0.00717 \text{ cases per person year}$$

$$\text{upper} = 0.00881 + 1.96\sqrt{7.657 \times 10^{-7}}$$

$$= 0.01060 \text{ cases per person year}$$

All the techniques for estimating incidence rate differences and summary incidence rate changes over strata are precisely analogous to those presented earlier for risks in closed cohort studies. The sole differences are to introduce incidence rate estimates (x/P) in the place of cumulative incidence estimates (x/N) and variance estimates for incidence rates (x/P^2) in the place of variance estimates for cumulative incidences ($x(N-x)/N^3$) in all the formulae.

It is common practice to examine the ratios of incidence rates in open cohort studies; this is the result of an empirical observation in chronic disease research, that incidence rate ratios tend to be more constant from study to study or from stratum to stratum of a single study than are rate differences. The easiest way to account for variability in incidence ratio estimates is on a logarithmic scale, in which the ratio estimate can be examined as a difference between the logarithms of the component incidence rate estimates. All of the foregoing procedures can then be adapted to confidence interval estimation on the log scale. Estimates, once obtained, are transformed back to the natural scale by exponentiation.

Denote the natural logarithm of the incidence rate estimate as $\ln(x/P)$. The variance of this quantity is approximately $1/x$. The variance of the logarithm of the incidence rate ratio is the sum of the variances of the logarithms of the component incidence rates.

Thus, to compare the lung cancer rate at 30-34 years after first exposure to that 20-24 years after first exposure, the procedure would be as follows:

$$RR = \left(\frac{103}{11,598}\right) / \left(\frac{57}{31,268}\right)$$

$$= 4.87$$

$$\ln(RR) = \ln(4.87)$$

$$= 1.5834$$

$$\text{Var}[\ln(RR)] = \frac{1}{103} + \frac{1}{57}$$

$$= 0.02725$$

The 95 percent confidence bounds for the logarithm of the ratio are

$$\text{lower} = 1.5834 - 1.96\sqrt{0.02725}$$

$$= 1.260$$

$$\text{upper} = 1.5834 + 1.96\sqrt{0.02725}$$

$$= 1.907$$

The 95 percent confidence bounds for the ratio are then

$$\text{lower} = \exp(1.260)$$

$$= 3.52$$

$$\text{upper} = \exp(1.907)$$

$$= 6.73$$

The ratio of lung cancer mortality rates for insulation workers 30-34 years from first exposure to asbestos to that 20-24 years from first exposure was approximately 4.9, with 95 percent confidence bounds of 3.5 and 6.7.

Stratified analysis. Two techniques are commonly used for summarizing incidence rate ratios across strata. Consider the hypothetical data in Table 8.1. The first subscript on the symbols displayed indicates the presence (1) or absence (0) of exposure, and the second subscript indicates the age group: 50-54 (1) or 55-59 (2).

Table 8.1 Lung cancer mortality in men exposed and unexposed to asbestos (hypothetical data)

	Age Group			
	50 - 54		55 - 59	
	Quantity	Symbol	Quantity	Symbol
Exposed				
Person Years	1,000	P_{11}	500	P_{12}
Cases	40	x_{11}	40	x_{12}
Unexposed				
Person Years	10,000	P_{01}	15,000	P_{02}
Cases	100	x_{01}	200	x_{02}

The summary technique most used in occupational health studies is to compare the number of cases of disease in the exposed group to that which would have been expected among the exposed, had the incidence rates observed in unexposed persons applied to those exposed. This expectation is obtained by multiplying the person years at risk in each stratum of the exposed group by the incidence rates observed in the unexposed group, and summing over all strata. Thus, in exposed workers,

$$\text{Observed} = x_{11} + x_{12}$$

$$= 40 + 40$$

$$= 80$$

$$\text{Expected} = P_{11}\frac{x_{01}}{P_{01}} + P_{12}\frac{x_{02}}{P_{02}}$$

$$= 1{,}000\left(\frac{100}{10{,}000}\right) + 500\left(\frac{200}{15{,}000}\right)$$

$$= 16.67$$

The ratio of observed to expected cases is designated (for historical reasons) as "the" *standardized mortality (or morbidity) ratio* (*SMR*). The ratio is standardized because it is algebraically identical to the ratio of age-standardized incidence rates in exposed and unexposed study subjects, taking for each the age distribution among exposed as the standard. In the present case

$$SMR = \frac{\text{Obs}}{\text{Exp}} = \frac{80}{16.67}$$

$$= 4.80$$

In practice, the *SMR* is rarely used except when the unexposed population is very large (most commonly a geographically defined population that encompasses the exposed persons). When the number of events is large in every stratum of the comparison population, the variance of the *SMR* is approximately Obs/Exp^2. In the present example

$$\text{Var}(SMR) = \frac{\text{Obs}}{\text{Exp}^2} = \frac{80}{(16.67)^2}$$

$$= 0.2880$$

The 95 percent confidence bounds can be obtained therefore as

$$\text{lower} = 4.800 - 1.96\sqrt{0.2880}$$

$$= 3.75$$

$$\text{lower} = 4.800 + 1.96\sqrt{0.2880}$$

$$= 5.85$$

When the sole source of stratum to stratum variation is thought to be random error, an incidence rate ratio estimate whose form is due to Mantel and Haenszel[60] is obtainable by summing the quantities

$$A_i = \frac{x_{1i}P_{0i}}{P_{1i} + P_{0i}} \qquad B_i = \frac{x_{0i}P_{1i}}{P_{1i} + P_{0i}}$$

over the strata, indexed here by i, and dividing the sums. In the present example,

60. The use of the procedure in open cohort studies was first proposed by Kenneth Rothman and John Boice. (Rothman KJ, Boice JR. Epidemiologic Analysis with a Programmable Calculator, NIH Publication No. 79-1649, Washington, 1979) The rationale was developed by David Clayton. (Clayton DG. The analysis of prospective studies of disease etiology. Commun Statist 1982;A11:2129-2155)

$$A = \sum_i A_i = \frac{(40)(10,000)}{10,000+1,000} + \frac{(40)(15,000)}{15,000+500}$$

$$= 75.07$$

$$B = \sum_i B_i = \frac{(100)(1,000)}{10,000+1,000} + \frac{(200)(500)}{15,000+500}$$

$$= 15.54$$

(When a variable, here i, appears below a sigma without any indication of the range of summation, the summation is taken over all possible values of the variable. In the present example, the possible values for i are 1 and 2.) The summary estimate, known as the *Mantel-Haenszel* estimate of the ratio is

$$RR_{MH} = \frac{A}{B}$$

$$= 4.831$$

The variance of the logarithm of the Mantel-Haenszel estimator is obtained by taking a further sum,

$$C = \sum_i (x_{1i} + x_{0i}) P_{1i} P_{0i} / (P_{1i} + P_{0i})^2$$

The variance estimate is then[61]

$$\text{Var}[\ln(RR_{MH})] \doteq \frac{C}{AB}$$

Here,

$$C = (40+100)(1,000)(10,000)/(1,000+10,000)^2$$

$$+ (40+200)(500)(15,000)/(500+15,000)^2$$

$$= 19.06$$

and

$$\text{Var}[\ln(RR_{MH})] \doteq \frac{19.06}{(75.07)(15.54)} = 0.01634$$

61. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41:55-68

The natural logarithm of the hazard ratio estimate is ln(4.831) = 1.575. Proceeding as before, the 95 percent confidence interval to the logarithm of the incidence rate ratio can be found to be 1.325 to 1.826, yielding a corresponding interval on the ratio scale of 3.8 to 6.2.

When the ratios observed in the strata being summarized are not very disparate, when the amounts of person time under study in each exposure group do not vary greatly across strata, or when the person time of the unexposed group is vastly larger than that of the exposed in each stratum, the *SMR* and the Mantel-Haenszel estimate of the incidence rate ratio will be very close to one another, and there is little practical distinction to be made between the two. In the last situation, the closeness of the Mantel-Haenszel estimator to the SMR arises from the fact that both procedures give weight in approximate proportion to the information contained in the exposed half of each stratum.[62] The theory underlying their respective derivations leads to a choice of the *SMR* whenever the stratum-specific hazard ratios are inconstant, and to the Mantel-Haenszel estimator when they do not vary greatly.

Case-Control Studies

Random Error. Analysis of the variability of odds ratios and of more complex functions involving odds ratios is almost always carried out on a logarithmic scale. Expressed as a logarithm, the odds ratio has a simple additive structure:

$$\ln(RR) = \ln\left(\frac{x_1 y_0}{y_1 x_0}\right)$$

$$= \ln(x_1) + \ln(y_0) - \ln(y_1) - \ln(x_0)$$

Here as before "ln(x)" stands for the natural logarithm of x.

An estimate of the variance of the logarithm of a count is given by[63]

62. Walker AM. Small sample properties of some estimators of a common hazard ratio. Appl Statistics 1985;34:42-8

63. The capital X in the formula is the random variable, of which the value x is the observed value.

$$\mathrm{Var}[\ln(X)] \doteq \frac{1}{x}$$

Let O stand for the parameter of which the odds ratio is an estimate. Since the variance of the sum or difference of terms equals the sum of the variances of the terms, we have an estimate of the variance of the logarithm of an odds ratio.

$$\mathrm{Var}[\ln(O)] = \mathrm{Var}[\ln(X_1)] + \mathrm{Var}[\ln(X_0)] + \mathrm{Var}[\ln(Y_1)] + \mathrm{Var}[\ln(Y_0)]$$

$$\doteq \frac{1}{x_1} + \frac{1}{x_0} + \frac{1}{y_1} + \frac{1}{y_0}$$

Approximate 95 percent confidence limits on the log scale are derived by subtracting 1.96 standard errors from $\ln(RR)$ to derive the lower limit, and adding (1.96 · SE) to $\ln(RR)$ to derive the upper limit. Finally, the confidence interval is expressed on the untransformed scale of the RR by exponentiating the limits just obtained.

Using the data from Example 6.1, the variance of the logarithm of the rate ratio is

$$\mathrm{Var}[\ln(RR)] = \frac{1}{17} + \frac{1}{2} + \frac{1}{579} + \frac{1}{600}$$

$$= 0.5622$$

The 95 percent confidence interval is

$$\text{lower} = \exp[\ln(8.808) - 1.96\sqrt{0.5622}]$$

$$= 2.026$$

$$\text{upper} = \exp[\ln(8.808) + 1.96\sqrt{0.5622}]$$

$$= 38.30$$

To two significant digits, the rate ratio is 8.8 with a 95 percent confidence interval of 2.0 to 38.

The dominant term in the variance estimate given above is due to the two controls with a history of undescended testis. Their contribution to the total estimated variance is so great that despite a relatively large number of exposed cases, the overall estimate of

effect remains very uncertain, as evidenced by the wide confidence interval. This example illustrates one of the limitations of case-control research: when the exposure under study is rare, estimates are likely to be highly unstable.

Analysis of Stratified Data. The most widely used estimate of a summary odds ratio over strata in a case-control study is that of Mantel and Haenszel.[64] The Mantel-Haenszel estimator provides a central value for the odds ratio to which each of the stratum-specific estimates contributes in approximate proportion to its own precision. It is calculated as follows. For each stratum i define the values x_{1i}, x_{0i}, y_{1i}, and y_{0i}, as above, and calculate their sum, T_i.

$$T_i = x_{1i} + x_{0i} + y_{1i} + y_{0i}$$

Now calculate two more derived quantities for each stratum, A_i and B_i.

$$A_i = \frac{x_{1i} y_{0i}}{T_i}$$

$$B_i = \frac{y_{1i} x_{0i}}{T_i}$$

Sum the values of A and B over the strata.

$$A = \sum_i A_i$$

$$B = \sum_i B_i$$

The Mantel-Haenszel summary estimate of the relative rate of disease over strata is

$$RR_{MH} = \frac{A}{B}$$

The parameter estimated by RR_{MH} is a postulated odds ratio that is common to all the strata. Under proper study design, this parameter is identical to the hazard ratio in the source population giving rise to cases and controls. As in the analysis of a single stratum, a confidence interval for the hazard ratio is best calculated on the

64. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48

logarithmic scale and then transformed back to the natural scale by exponentiation. In order to obtain an estimate of the variance of the estimator $\ln(RR_{MH})$, it is necessary to calculate several further quantities for each stratum.[65]

$$C_i = \frac{x_{1i} + y_{0i}}{T_i}$$

$$D_i = \frac{y_{1i} + x_{0i}}{T_i}$$

The four derived quantities are combined and summed, stratum by stratum, as follows:

$$(AC) = \sum_i A_i C_i$$

$$(AD) = \sum_i A_i D_i$$

$$(BC) = \sum_i B_i C_i$$

$$(BD) = \sum_i B_i D_i$$

The variance of $\ln(RR_{MH})$ is, approximately,

$$\mathrm{Var}[\ln(RR_{MH})] \doteq \frac{1}{2}\left[\frac{(AC)}{A^2} + \frac{(AD)+(BC)}{AB} + \frac{(BD)}{B^2}\right]$$

As before, the standard error is calculated as the square root of the variance, and 95 percent confidence intervals are obtained on the logarithmic scale by adding and subtracting 1.96 times the standard error to $\ln(RR_{MH})$, after which all of these are transformed back to the original rate ratio scale.

At first glance, the calculation of the 95 percent confidence interval seems a burdensome job, and it does entail a good deal of arithmetic when carried out by hand. An important feature of the formulas is that the data from each stratum need to be processed only once and added to the various accumulating terms. Repeated stratum-by-stratum accumulations are readily accommodated in

65. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol 1986;124:719-23

spreadsheet programs and programmable calculators. When there is only one stratum, all the above formulas simplify to those given previously for the unstratified case.

Example 8.1. *Body mass index and the relative incidence of breast cancer.*[66]

> Seventy-two premenopausal women with breast cancer newly diagnosed at the Group Health Cooperative of Puget Sound from July 1975 through June 1978 were interviewed, along with 80 premenopausal women from the same HMO who were hospitalized with a variety of acute conditions. For each subject, the body mass index was ascertained. Women with a body mass index (weight in kilograms divided by the square of height in meters) greater than 28 were classified as "heavy." The first two panels on the left side of Table 8.2 give the distribution of study subjects over categories of disease status, age, and body mass index, together with the age-specific estimates of the rate ratio and the 95 percent confidence intervals.

Calculated values for each of the quantities necessary for the summary estimate of the rate ratio and for the corresponding 95 percent confidence intervals are shown in the right hand panels of Table 8.2, and the resulting estimates are shown in the lower left. Heavy women appear to be at lower risk of breast cancer in both age groups than are other women. Both age-specific estimates are very unstable, because of the small number of heavy women in the study, and particularly so because of the paucity of heavy cases. The common estimate, which accumulates the information available from both strata, is more precise than either of the component values. Note that the common estimate lies within the range of the stratum-specific estimates, as will always be the case.

66. Jick H, Walker AM, Watkins RN, D'Ewart D, et al. Oral contraceptives and breast cancer. Am J Epidemiol 1980;112:577-85

Table 8.2 Body mass index and the relative incidence of breast cancer among premenopausal women *Calculation of table-specific and summary measures for a case-control study*

Age ≤ 45	Heavy	Not Heavy		
			$T_1 = 78$	
			$A_1 = 0.7692$	$A_1C_1 = 0.3156$
Breast Ca	2	35	$B_1 = 0.4103$	$A_1D_1 = 0.4536$
			$C_1 = 4.9359$	$B_1C_1 = 2.0250$
Controls	11	30	$D_1 = 0.5897$	$B_1D_1 = 2.9109$

$RR = 0.16$
95% CI = 0.032 - 0.76

Variance of ln(RR) = 0.6528

Age > 45	Heavy	Not Heavy		
			$T_2 = 73$	
			$A_2 = 0.8767$	$A_2C_2 = 0.4083$
Breast Ca	2	33	$B_2 = 2.7123$	$A_2D_2 = 0.4684$
			$C_2 = 0.4658$	$B_2C_2 = 1.2633$
Controls	6	32	$D_2 = 0.5342$	$B_2D_2 = 1.4491$

$RR = 0.32$
95% CI = 0.061 - 1.7

Variance of ln(RR) = 0.7282

Summary			
	$A = 1.6459$	$AC = 0.7239$	
	$B = 7.6482$	$AD = 0.9220$	
$RR_{MH} = 0.22$		$BC = 3.2883$	
95% CI = 0.069 - 0.67		$BD = 4.3600$	

Variance of ln(RR) = 0.3381