

## 16: Risk Ratios

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### Introduction

This chapter concentrates on risk ratio and prevalence ratios. Both risk ratios and prevalence ratios are ratios of proportions. When comparing proportion from independent groups, we adopt the following notation:

	<b>Disease +</b>	<b>Disease -</b>	
<b>Exposure +</b>	$A_1$	$B_1$	$N_1$
<b>Exposure -</b>	$A_0$	$B_0$	$N_0$
	$M_1$	$M_0$	$N$

In this notation,  $A$  indicates “case” and  $B$  indicates “noncase.” Subscript  $_1$  denotes “exposed” and subscript  $_0$  denotes “non-exposed.” For example,  $A_1$  indicates the number of exposed cases and  $B_0$  indicates the number of non-exposed non-cases. There are  $N_1$  exposed individuals and  $N_0$  non-exposed individuals. There are  $N$  individuals in the study.

Let  $\hat{p}_1$  represent the incidence proportion (risk) estimator in the exposed group, and let  $\hat{p}_0$  represent the risk

estimator in the nonexposed group:  $\hat{p}_1 = \frac{A_1}{N_1}$  and  $\hat{p}_0 = \frac{A_0}{N_0}$ .

Let  $\phi$  (lowercase phi) represent the **risk ratio parameter** and  $\hat{\phi}$  (phi hat) represent the **risk ratio estimator**:

$$\hat{\phi} = \frac{\hat{p}_1}{\hat{p}_0} \tag{1}$$

The above formulas apply to prevalences as well, in which case  $p_1$  represents the prevalence in the exposed group,  $p_0$  represents the prevalence in the nonexposed group, and  $\phi$  represents the **prevalence ratio parameter**. The prevalence ratio is equal to the risk ratio when (a) the average duration of disease is the same in the groups, (b) the disease is “rare” (say, risk  $\leq 5\%$ ), and (c) the disease does not influence the presence of the exposure.

**Illustrative example (toxic .sav).** A chemotherapeutic agent used for bone marrow ablation in preparation for transplantation comes in either generic or non-generic form. Patients at a particular hospital

received either the generic or non-generic formulation.\* The study outcome was cerebellar toxicity. Cross-tabulation revealed:

	Toxicity +	Toxicity	
Generic +	11	14	25
Generic	3	31	34
	14	31	59

Thus,  $\hat{p}_1 = \frac{11}{25} = .440$ ,  $\hat{p}_0 = \frac{3}{34} = .0882$ , and  $\hat{\phi} = \frac{.440}{.0882} = 4.99$ .

**Interpretation:** The risk ratio of 4.99 (about 5) indicates that risk in the exposed group is 5-times that of the non-exposed group. The segment of the risk ratio above (or below) 1 quantifies the relative increase (or decrease) in risk associated with exposure. For example, the risk ratio of 5 reveals a  $5 - 1.00 = 400(100\%) = 400\%$  increase in risk with exposure.

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\* Jolson, H. M., Bosco, L., Bufton, M. G., Gerstman, B. B., Rinsler, S. S., Williams, E., et al. (1992). Clustering of adverse drug events: analysis of risk factors for cerebellar toxicity with high-dose cytarabine. *JNCI*, 84, 500-505.

## Confidence Interval for the Risk Ratio

To calculate a 95% confidence interval for the risk ratio parameter, convert the risk ratio estimate to a *natural log* (ln) scale. (Use the ln key or “inverse  $e$ ” key on your calculator.) For the illustrative data, the natural log of the risk ratio =  $\ln(4.99) = 1.607$ .

The **standard error of the natural log of the risk ratio** is

$$se_{\ln \hat{\phi}} = \sqrt{\frac{1 - \hat{p}_1}{N_1 \hat{p}_1} + \frac{1 - \hat{p}_0}{N_0 \hat{p}_0}} \quad (2)$$

and a **95% confidence interval for the  $\ln \phi$**  is

$$\ln \hat{\phi} \pm (1.96)(se_{\ln \hat{\phi}}) \quad (3)$$

We then take **antilogs** of these limits to convert them to a non-logarithmic scale. (The antilog key on your calculator might be labeled  $e$ , for “exponent,” or you might have to use the inverse- $\ln x$  key.)

**Illustrative example.** For the illustrative data,  $se_{\ln \hat{\phi}} = \sqrt{\frac{1 - .4400}{(25)(.4400)} + \frac{1 - .0882}{(24)(.0882)}} = 0.5964$ . A **95% confidence interval** for  $\ln \phi = 1.607 \pm (1.96)(0.5964) = 1.607 \pm 1.169 = (0.4381, 2.779)$ . The 95% CI for  $\phi = e^{(0.4381, 2.779)} = (1.55, 16.05)$ , giving us a better idea of what might be in the population. To calculate a **90% confidence interval**, change the 1.96 in formula 3 to 1.645. A 90% confidence interval for  $\ln \phi = 1.607 \pm (1.645)(0.5964) = 1.607 \pm 0.981 = (0.626, 2.588)$ . The 90% confidence interval for  $\phi = e^{(0.626, 2.588)} = (1.87, 13.30)$ .

**Assumptions:** The interpretation of statistics requires assumptions. Distributional assumptions for the above formulas are based on a normal sampling distribution. Normality can be assumed when expected values in the table are at least 5. Validity assumptions require no information bias, no selection bias, and no confounding, as discussed in prior chapters.

## *p* Value

### Chi-Square with Continuity Correction

The test for  $H_0: \phi = 1$  can be performed with the chi-square test introduced in Chapter 10. That test was called the Pearson's's uncorrected chi-square test. We now introduce Yates' continuity corrected chi-square.

As with the uncorrected chi-square statistic, the **continuity corrected chi-square test** begins by calculating expected frequencies under the null hypothesis as product of table margins divided by the total. For the illustrative data, expected frequencies are:

	Disease +	Disease	
Exposure +	5.93*	19.07	25
Exposure	8.07	25.93	34
	14	45	59

The **continuity-corrected chi-square statistic** is

$$\chi_{Yates}^2 = \sum \frac{(|O_i - E_i| - 0.5)^2}{E_i} \quad (4)$$

where  $O_i$  represents the observed frequency in cell  $i$   $E_i$  represents the expected frequency, and  $|O_i - E_i|$  is the *absolute value* of the difference of the observed and expected. With 2-by-2 tables, this statistic has 1 degree of freedom. For the illustrative data,

$$\begin{aligned} \chi_{Yates}^2 &= (|11 - 5.93| - .5)^2/5.93 + (|14 - 19.07| - .5)^2/19.07 + (|3 - 8.07| - .5)^2/8.07 + (|31 - 25.93| - .5)^2/25.93 \\ &= (|5.07| - .5)^2/5.93 + (|-5.07| - .5)^2/19.07 + (|-5.07| - .5)^2/8.07 + (|5.07| - .5)^2/25.93 \\ &= 4.57^2/5.93 + 4.57^2/19.07 + 4.57^2/8.07 + 4.57^2/25.93 \\ &= 3.52 + 1.10 + 2.59 + 0.81 \\ &= 8.02. \end{aligned}$$

This statistic has 1 degree of freedom.

**Relation between  $\chi_{stat}^2$  with 1 df and the Z distribution.** For 2-by-2 cross-tabulated data, you can take the square root of the chi-square statistic. This is now a  $\chi$  (chi) statistic. The chi-statistic has a standard normal (z) distribution under  $H_0$  and can thus be converted to a two-tailed  $p$  value with the two-tailed  $Z$  table available in the back of this Reader. For the illustrative data,  $\chi_{stat} = \sqrt{\chi_{stat}^2} = \sqrt{8.02} = 2.83$ . We determine  $p = .00465$  from the table in the back of the book.

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\* The expected frequency in cell  $A_1 = (25)(14)/(59) = 5.93$

## Fisher's Exact Test

Chi-square tests must be avoided when an expected frequency in the 2-by-2 table is less than 5. In such instances, a procedure based on exact probabilities is needed. One such procedure is Fisher's test.

Fisher's exact test is based on summing exact probabilities for table permutations that are more extreme than current data. We will not cover the calculation method, opting instead for calculation with SPSS, WinPepi, or EpiCalc2000.

**Illustrative example (*kxnecro.sav*).** Data on post-operative colonic necrosis following use of Kayexelate™ are shown below.\*

	Disease +	Disease	
Exposure +	2	115	117
Exposure	0	862	862
	2	977	979

Expected frequencies are:

	Disease +	Disease	
Exposure +	0.24 <sup>†</sup>	116.76	117
Exposure	1.76	860.24	862
	2	977	979

Because two of cells have expectations that are less than 5, the chi-square test is avoided and Fisher's exact test is used. Using WinPepi, we derive a two-tailed Fishers *p* value of .014.

**Computation.** In SPSS, click Analyze > Descriptive Statistics > Crosstabs. Select the exposure variable as the row variable and the disease variable as the column variable. Then click Statistics button > risk box > OK. To calculate chi-square and Fisher's test, click the Statistics button and check the Chi-square box. In *WinPepi* use COMPARE2 .EXE > A or B. In *EpiCalc2000*, select Tables > 2-by-2 unstratified.

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\* Gerstman, B. B., Kirkman, R., & Platt, R. (1992). Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *American Journal of Kidney Diseases*, 20, 159-161.

† The expected frequency in cell  $A_1 = (117)(2) / (979) = 0.24$

## Sample Size Requirements

The sample size requirements of a study of risk ratios can be addressed by considering: (A) the sample size required for a significant test when a true risk ratio greater of a given magnitude exists at a given significance level and power or (B) the sample required to satisfy a required precision (i.e., provide a confidence interval of a given width). Let us consider techniques for (A) before moving to (B).

Recall that the **significance level** ( $\alpha$ ) of a fixed-level test is the probability of a type I error (false rejection of the null) and **power** ( $1 - \beta$ ) is the probability of avoiding a type II error (false retention of the null). Also recall that we have two competing hypotheses:  $H_0: \phi = 1$  versus  $H_1: \phi = \text{something else}$ . Let  $\phi_1$  denote this something else, which we call the **expected risk ratio under the alternative hypothesis**.

We use WinPepi > COMPARE2.EXE. to calculate results. Click the Sample size menu (on top) and then choose the Proportions (simple comparisons) option. The desired level of significance (e.g.,  $\alpha = .05$  two-sided), power (e.g.,  $1 - \beta = .90$ ), and expected value of the risk ratio under the alternative hypothesis (e.g.,  $\phi_1 = 2.0$ ) are entered into the program. In addition, the relative sizes of the groups (e.g.,  $N_0/N_1 = 1$ )\* must be entered, as must the assumed proportion in the non-exposed group (e.g.,  $p_0 = .10$ ). Clicking "Run" provides results for uncorrected (Pearson's) and continuity corrected (Yates') chi-square testing.

**Illustrative example.** Using the parenthetical assumptions in the prior paragraph derives the following output:

The screenshot shows the 'Compare 2' dialog box in WinPepi. The title bar reads 'Compare 2'. The menu bar includes 'Compare', 'Misc', 'Sample size', 'Power', 'Note', 'View', 'Save', 'Help', and 'Quit'. The main window title is 'Sample sizes needed to test a difference between 2 independent samples'. A yellow box contains the instruction: 'FIRST CLICK ON TYPE OF COMPARISON'. Below this, a list of comparison types is shown, with 'Proportions (simple comparison)' selected. To the right, a yellow box explains: 'The groups are A and B. In a case-control study or trial, call the controls "B". In a cohort study, call the unexposed "B".'. Input fields show: Significance level %: 5, Power %: 90, Ratio of sample sizes B:A: 1, and Proportion in B: .1. The 'TO DETECT' section shows: Odds ratio A:B: [blank], Ratio A:B: 2, and Proportion in A: 0.20. The results section displays: REQUIRED SAMPLE: Total 532 (266 in A, 266 in B); Continuity-corrected: Total 572 (286 in A, 286 in B); EXPECTED PRECISION: Approx. 95% CI for difference between proportions (D) = D - 0.061 to D + 0.061. Buttons for 'Clear', 'Repeat', 'Run', and 'Print' are at the bottom.

Thus, we need a total sample size of 572 when using the continuity corrected test.

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\* WinPepi calls the non-exposed group B and exposed group A