

Chapter 208

Confidence Intervals for the Odds Ratio of Two Proportions using an Unmatched Case-Control Design

Introduction

This routine calculates the group sample sizes necessary to achieve a specified confidence interval width of the odds ratio (OR) from data collected using an unmatched case-control design. Such a design is used for retrospective studies.

OR is calculated as

$$OR = \frac{p_1(1 - p_2)}{p_2(1 - p_1)}$$

where p_1 and p_2 are the *probabilities of exposure* among cases (disease) and controls (no disease), respectively.

This routine is partially based on O'Neill (1988). This paper provides a useful overview of the vaccine efficacy studies, the assumptions that are made, and discussion of when this design is useful. We highly recommend it.

Technical Details

This section will review the details of calculating sample sizes for the odds ratio of two proportions in case-control designs.

Comparing Two Proportions

Suppose you have two populations from which dichotomous (binary) responses will be recorded. The probability of obtaining an event of interest (risk factor exposure) in population 1 (the case group) is p_1 and in population 2 (the control group) is p_2 . The risk factor is a dichotomous variable that represents a variable (vaccination, smoking status, etc.) that is thought to be related to the outcome (disease or no-disease). The corresponding failure probabilities are given by $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

The assumption is made that the responses from each group follow a binomial distribution. This means that the event probability p_i is the same for all subjects within a population and that the responses from one subject to the next are independent of one another.

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Random samples of n_1 and n_2 individuals are obtained from these two populations. The data from these samples can be displayed in a 2-by-2 contingency table as follows

	Cases	Controls	Total
Vaccinees	x_{11}, a	x_{12}, b	m_1
Controls	x_{21}, c	x_{22}, d	m_2
Totals	n_1, m	n_2, n	N

The binomial proportions are estimated from these data using the formulae

$$\hat{p}_1 = \frac{x_{11}}{n_1} \quad \text{and} \quad \hat{p}_2 = \frac{x_{12}}{n_2}$$

In this procedure, our attention will focus on using the odds ratio to compare the two binomial proportions. The odds ratio is given by $\psi = (p_1/q_1)/(p_2/q_2)$ which gives the relative change in the odds of exposure to the risk factor among the cases to the odds of the controls.

Although the odds ratio is more complicated than the simple risk ratio of the disease attack rates, it is used in this case because a direct estimate of the ratio of the attack rates is not available in a case-control design. In this case, it is hoped that the odds ratio will provide a reasonable approximation of the risk ratio of the attack rates.

Confidence Intervals for the Odds Ratio

Many methods have been devised for computing confidence intervals for the odds ratio of two proportions. Eight of these methods are available in this procedure. They are

1. Exact (Conditional)
2. Score (Farrington and Manning)
3. Score (Miettinen and Nurminen)
4. Fleiss
5. Logarithm
6. Mantel-Haenszel
7. Simple
8. Simple + 1/2

Conditional Exact

The conditional exact confidence interval of the odds ratio is calculated using the noncentral hypergeometric distribution as given in Sahai and Khurshid (1995). That is, a $100(1 - \alpha)\%$ confidence interval is found by searching for ψ_L and ψ_U such that

$$\frac{\sum_{k=x}^{k_2} \binom{n_1}{k} \binom{n_2}{m_1 - k} (\psi_L)^k}{\sum_{k=k_1}^{k_2} \binom{n_1}{k} \binom{n_2}{m_1 - k} (\psi_L)^k} = \frac{\alpha}{2}$$

and

$$\frac{\sum_{k=k_1}^x \binom{n_1}{k} \binom{n_2}{m_1 - k} (\psi_U)^k}{\sum_{k=k_1}^{k_2} \binom{n_1}{k} \binom{n_2}{m_1 - k} (\psi_U)^k} = \frac{\alpha}{2}$$

where

$$k_1 = \max(0, m_1 - n_1) \text{ and } k_2 = \min(n_1, m_1)$$

Farrington and Manning's Score

Farrington and Manning (1990) developed a test statistic similar to that of Miettinen and Nurminen but with the factor $N/(N-1)$ removed.

The formula for computing this test statistic is

$$Z_{FMO} = \frac{\frac{(\hat{p}_1 - \tilde{p}_1)}{\tilde{p}_1 \tilde{q}_1} - \frac{(\hat{p}_2 - \tilde{p}_2)}{\tilde{p}_2 \tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1 \tilde{p}_1 \tilde{q}_1} + \frac{1}{n_2 \tilde{p}_2 \tilde{q}_2}\right)}}$$

where the estimates \tilde{p}_1 and \tilde{p}_2 are computed as in the corresponding test of Miettinen and Nurminen (1985) as

$$\tilde{p}_1 = \frac{\tilde{p}_2 \psi_0}{1 + \tilde{p}_2 (\psi_0 - 1)}$$

$$\tilde{p}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$A = n_2(\psi_0 - 1)$$

$$B = n_1 \psi_0 + n_2 - m_1(\psi_0 - 1)$$

$$C = -m_1$$

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Farrington and Manning (1990) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{FMO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{FMO} = -|z_{\alpha/2}|$$

Miettinen and Nurminen's Score

Miettinen and Nurminen (1985) proposed a test statistic for testing whether the odds ratio is equal to a specified value ψ_0 . Because the approach they used with the difference and ratio does not easily extend to the odds ratio, they used a score statistic approach for the odds ratio. The regular MLE's are \hat{p}_1 and \hat{p}_2 . The constrained MLE's are \tilde{p}_1 and \tilde{p}_2 . These estimates are constrained so that $\tilde{\psi} = \psi_0$. A correction factor of $N/(N-1)$ is applied to make the variance estimate less biased. The significance level of the test statistic is based on the asymptotic normality of the score statistic.

The formula for computing the test statistic is

$$z_{MNO} = \frac{\frac{(\hat{p}_1 - \tilde{p}_1)}{\tilde{p}_1 \tilde{q}_1} - \frac{(\hat{p}_2 - \tilde{p}_2)}{\tilde{p}_2 \tilde{q}_2}}{\sqrt{\left(\frac{1}{n_1 \tilde{p}_1 \tilde{q}_1} + \frac{1}{n_2 \tilde{p}_2 \tilde{q}_2}\right) \left(\frac{N}{N-1}\right)}}$$

where

$$\tilde{p}_1 = \frac{\tilde{p}_2 \psi_0}{1 + \tilde{p}_2 (\psi_0 - 1)}$$

$$\tilde{p}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

$$A = n_2(\psi_0 - 1)$$

$$B = n_1 \psi_0 + n_2 - m_1(\psi_0 - 1)$$

$$C = -m_1$$

Miettinen and Nurminen (1985) proposed inverting their score test to find the confidence interval. The lower limit is found by solving

$$z_{MNO} = |z_{\alpha/2}|$$

and the upper limit is the solution of

$$z_{MNO} = -|z_{\alpha/2}|$$

Iterated Method of Fleiss

Fleiss (1981) presents an improved confidence interval for the odds ratio. This method forms the confidence interval as all those values of the odds ratio which would not be rejected by a chi-square hypothesis test. Fleiss gives the following details about how to construct this confidence interval. To compute the lower limit, do the following.

1. For a trial value of ψ , compute the quantities X , Y , W , F , U , and V using the formulas

$$X = \psi(m + s) + (n - s)$$

$$Y = \sqrt{X^2 - 4ms\psi(\psi - 1)}$$

$$A = \frac{X - Y}{2(\psi - 1)}$$

$$B = s - A$$

$$C = m - A$$

$$D = f - m + A$$

$$W = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$$

$$F = \left(a - A - \frac{1}{2}\right)^2 W - z_{\alpha/2}^2$$

$$T = \frac{1}{2(\psi - 1)^2} \left(Y - n_{..} - \frac{\psi - 1}{Y} [X(m + s) - 2ms(2\psi - 1)] \right)$$

$$U = \frac{1}{B^2} + \frac{1}{C^2} - \frac{1}{A^2} - \frac{1}{D^2}$$

$$V = T \left[\left(a - A - \frac{1}{2}\right)^2 U - 2W \left(a - A - \frac{1}{2}\right) \right]$$

Finally, use the updating equation below to calculate a new value for the odds ratio using the updating equation

$$\psi^{(k+1)} = \psi^{(k)} - \frac{F}{V}$$

2. Continue iterating until the value of F is arbitrarily close to zero.

The upper limit is found by substituting $+\frac{1}{2}$ for $-\frac{1}{2}$ in the formulas for F and V .

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Confidence limits for the *relative risk* can be calculated using the expected counts A , B , C , and D from the last iteration of the above procedure. The lower limit of the relative risk

$$\phi_{lower} = \frac{A_{lower}n}{B_{lower}m}$$

$$\phi_{upper} = \frac{A_{upper}n}{B_{upper}m}$$

Mantel-Haenszel

The common estimate of the logarithm of the odds ratio is used to create this estimator. That is

$$\ln(\hat{\psi}) = \ln\left(\frac{ad}{bc}\right)$$

The standard error of this estimator is estimated using the Robins, Breslow, Greenland (1986) estimator, which performs well in most situations. The standard error is given by

$$se(\ln(\hat{\psi})) = \sqrt{\frac{A}{2C} + \frac{AD + BC}{2CD} + \frac{B}{2D}}$$

where

$$A = \frac{a + d}{N}$$

$$B = \frac{b + c}{N}$$

$$C = \frac{ad}{N}$$

$$D = \frac{bc}{N}$$

The confidence limits are calculated as

$$\hat{\psi}_{lower} = \exp\left(\ln(\hat{\psi}) - z_{1-\frac{\alpha}{2}}se(\ln(\hat{\psi}))\right)$$

$$\hat{\psi}_{upper} = \exp\left(\ln(\hat{\psi}) + z_{1-\alpha/2}se(\ln(\hat{\psi}))\right)$$

Simple, Simple + ½, and Logarithm

The simple estimate of the odds ratio uses the formula

$$\begin{aligned}\hat{\psi} &= \frac{\hat{p}_1 \hat{q}_2}{\hat{p}_2 \hat{q}_1} \\ &= \frac{ad}{bc}\end{aligned}$$

The standard error of this estimator is estimated by

$$se(\hat{\psi}) = \hat{\psi} \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

Problems occur if any one of the quantities a , b , c , or d are zero. To correct this problem, many authors recommend adding one-half to each cell count so that a zero cannot occur. Now, the formulas become

$$\hat{\psi}' = \frac{(a + 0.5)(d + 0.5)}{(b + 0.5)(c + 0.5)}$$

and

$$se(\hat{\psi}') = \hat{\psi}' \sqrt{\frac{1}{a + 0.5} + \frac{1}{b + 0.5} + \frac{1}{c + 0.5} + \frac{1}{d + 0.5}}$$

The distribution of these direct estimates of the odds ratio does not converge to normality as fast as does their logarithm, so the logarithm of the odds ratio is used to form confidence intervals. The formula for the standard error of the log odds ratio is

$$L' = \ln(\hat{\psi}')$$

and

$$se(L') = \sqrt{\frac{1}{a + 0.5} + \frac{1}{b + 0.5} + \frac{1}{c + 0.5} + \frac{1}{d + 0.5}}$$

A $100(1 - \alpha)\%$ confidence interval for the log odds ratio is formed using the standard normal distribution as follows

$$\hat{\psi}_{lower} = \exp\left(L' - z_{1-\alpha/2} se(L')\right)$$

$$\hat{\psi}_{upper} = \exp\left(L' + z_{1-\alpha/2} se(L')\right)$$

See Fleiss et al (2003) for more details.

Sample Size Estimation

Sample size estimation is straight forward. For each method, anticipated (planned) values of the two probabilities are substituted for the estimated values given in the above formulas, along with the sample sizes of each of the groups and the confidence level. The width between the two limits becomes the measure of precision. The more narrow the confidence interval, the more precise it is.

To find an appropriate sample size for a given set of parameters, a binary search is conducted for the smallest sample size that meets the width requirements.

Confidence Level

The confidence level, $1 - \alpha$, has the following interpretation. If thousands of random samples of size n_1 and n_2 are drawn from populations 1 and 2, respectively, and a confidence interval for the true difference/ratio/odds ratio of proportions is calculated for each pair of samples, the proportion of those intervals that will include the true difference/ratio/odds ratio of proportions is $1 - \alpha$.

Example 1 – Calculating Sample Size

Suppose a study is planned in which the researcher wishes to construct a two-sided 95% confidence interval for the odds ratio such that the width of the interval is no wider than 0.2. Additional widths of 0.15 and 0.25 are also to be investigated. The confidence interval method to be used is the Mantel-Haenszel method. The confidence level is set to 0.95. OR is set at 0.7 and 0.8. P2 is 0.06. A case-control design is planned in which there will be four controls chosen for each case.

The goal is to determine the necessary sample size.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For	Sample Size
Method.....	Mantel-Haenszel
Interval Type	Two-Sided
Confidence Level (1 - α)	0.95
Group Allocation	Enter R = N2/N1, solve for N1 and N2
R (Group Sample Size Ratio)	4
W (Confidence Interval Width)	0.15 0.2 0.25
Odds Ratio Input Type	Enter OR and P2
OR (Odds Ratio)	0.7 0.8
P2 (Probability of Exposure in Controls)	0.06

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Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results

Solve For: Sample Size
Interval Type: Two-Sided
Confidence Interval Method: Mantel-Haenszel

Confidence Level 1 - α	Sample Size					Confidence Interval Width		Probability of Exposure		Odds Ratio OR	Confidence Interval Limits of OR	
	Case N1	Control N2	Total N	Target R	Actual R	Target W _T	Actual W _A	Case P1	Control P2		Lower LCL	Upper UCL
0.95	9694	38776	48470	4	4	0.15	0.15000	0.04277	0.06	0.7	0.62901	0.77901
0.95	5469	21876	27345	4	4	0.20	0.20000	0.04277	0.06	0.7	0.60711	0.80711
0.95	3514	14056	17570	4	4	0.25	0.24997	0.04277	0.06	0.7	0.58608	0.83606
0.95	11427	45708	57135	4	4	0.15	0.15000	0.04858	0.06	0.8	0.72851	0.87851
0.95	6442	25768	32210	4	4	0.20	0.20000	0.04858	0.06	0.8	0.70623	0.90623
0.95	4135	16540	20675	4	4	0.25	0.24999	0.04858	0.06	0.8	0.68471	0.93470

1 - α	The Confidence Level. The proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the true value of OR.
N1	The number of subjects sampled from the population of cases.
N2	The number of subjects sampled from the population of controls.
N	The total sample size. $N = N1 + N2$.
Target R	The desired sampling ratio. $R = N2 / N1$ or $N2 = R(N1)$. Often, R is labelled 'C' in the case-control literature.
Actual R	The actual sampling ratio. $R = N2 / N1$ or $N2 = R(N1)$. Because N1 and N2 are discrete, this value is sometimes slightly different from the target R.
W _T	The target width of the confidence interval of OR.
W _A	The actual width of the confidence interval of OR that was computed by the procedure.
P1	The probability of having been vaccinated (vaccine prevalence) in the case group.
P2	The probability of having been vaccinated (vaccine prevalence) in the control group.
OR	The Odds Ratio of the exposure probability of cases and the exposure probability of controls.
LCL	The lower confidence interval limit of OR.
UCL	The upper confidence interval limit of OR.

Summary Statements

An unmatched case-control design will be used to obtain a two-sided 95% confidence interval for the odds ratio of two proportions (odds[Cases] / odds[Controls]). The probability of exposure among the controls is assumed to be 0.06 and the probability of exposure among the cases is assumed to be 0.04277 (odds ratio = 0.7). The Mantel-Haenszel method will be used to compute the confidence interval limits. To produce a confidence interval width of 0.15, the number of subjects needed will be 9694 in the case group and 38776 in the control group.

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Dropout-Inflated Sample Size

Dropout Rate	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
	N1	N2	N	N1'	N2'	N'	D1	D2	D
20%	9694	38776	48470	12118	48470	60588	2424	9694	12118
20%	5469	21876	27345	6837	27345	34182	1368	5469	6837
20%	3514	14056	17570	4393	17570	21963	879	3514	4393
20%	11427	45708	57135	14284	57135	71419	2857	11427	14284
20%	6442	25768	32210	8053	32210	40263	1611	6442	8053
20%	4135	16540	20675	5169	20675	25844	1034	4135	5169

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N1, N2, and N	The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.
N1', N2', and N'	The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas $N1' = N1 / (1 - DR)$ and $N2' = N2 / (1 - DR)$, with N1' and N2' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D1, D2, and D	The expected number of dropouts. $D1 = N1' - N1$, $D2 = N2' - N2$, and $D = D1 + D2$.

Dropout Summary Statements

Anticipating a 20% dropout rate, 12118 subjects should be enrolled in Group 1, and 48470 in Group 2, to obtain final group sample sizes of 9694 and 38776, respectively.

References

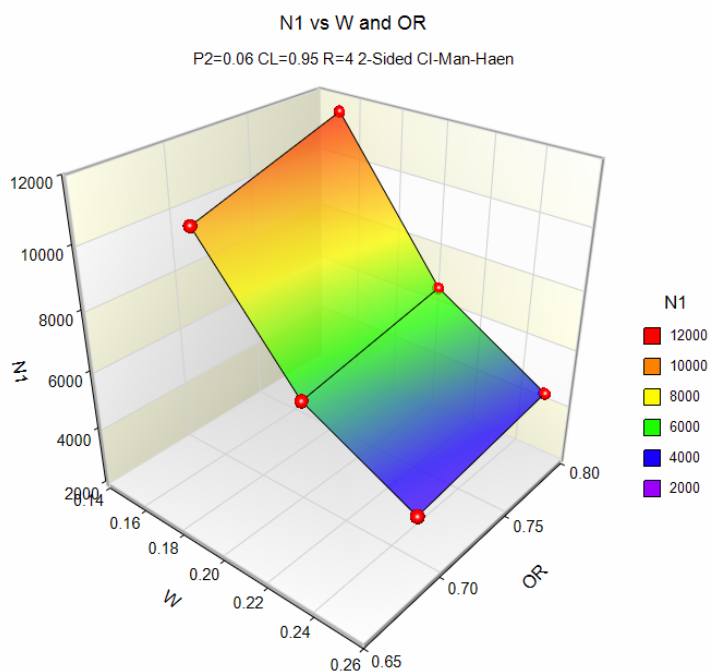
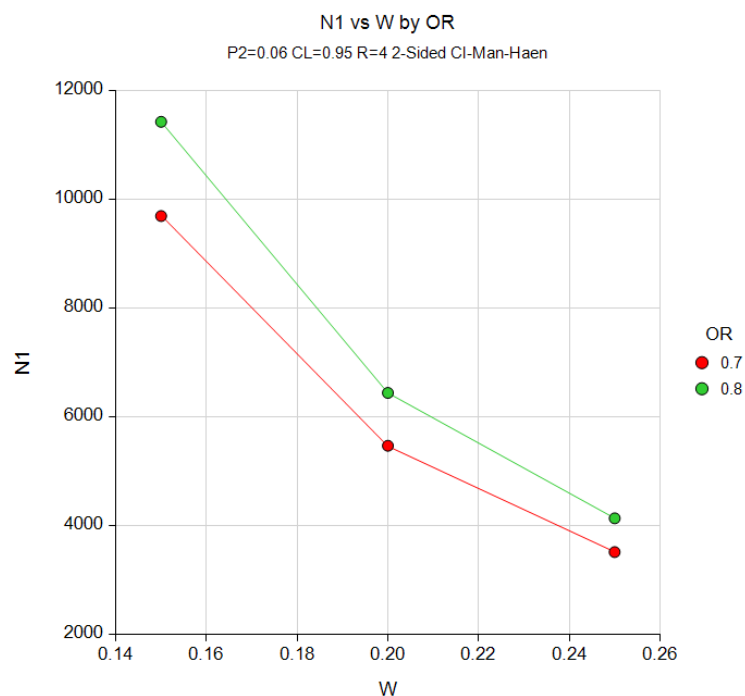
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This report shows the calculated sample sizes for each of the scenarios.

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Plots Section

Plots



These plots show the group sample size versus the confidence interval width for the two OR values.

Example 2 – Validation using O'Neill (1988)

O'Neill (1988) page 1286 gives an example of a sample size calculation for a confidence interval for OR when the confidence level is 95%, OR = 0.2 (VE is 0.8), P2 is 0.2, and the desired width is 0.24. The confidence interval method is Mantel-Haenszel. The design calls for 4 controls for each case. The sample size in from the cases is 280.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab

Solve For **Sample Size**
 Method..... **Mantel-Haenszel**
 Interval Type **Two-Sided**
 Confidence Level (1 - α) **0.95**
 Group Allocation **Enter R = N2/N1, solve for N1 and N2**
 R (Group Sample Size Ratio) **4**
 W (Confidence Interval Width) **0.24**
 Odds Ratio Input Type **Enter OR and P2**
 OR (Odds Ratio) **0.2**
 P2 (Probability of Exposure in Controls) **0.2**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results

Solve For: [Sample Size](#)
 Interval Type: Two-Sided
 Confidence Interval Method: Mantel-Haenszel

Confidence Level 1 - α	Sample Size					Confidence Interval Width		Probability of Exposure		Odds Ratio OR	Confidence Interval Limits of OR	
	Case N1	Control N2	Total N	Target R	Actual R	Target Wt	Actual WA	Case P1	Control P2		Lower LCL	Upper UCL
0.95	281	1124	1405	4	4	0.24	0.23969	0.04762	0.2	0.2	0.11331	0.353

PASS has also computed an N1 of 281, which is just slightly above the 280 in the article. This difference arises because of rounding.