Chapter 863

Tests for the Interaction Odds Ratio in Logistic Regression with Two Binary X's (Wald Test)

Introduction

Logistic regression expresses the relationship between a binary response variable and one or more independent variables called *covariates*. This procedure is for the case when there are two binary covariates (X and Z) and their interaction in the logistic regression model and a Wald test of the interaction is used. Often, Y is called the *response* variable, the first binary covariate, X, is referred to as the *exposure* variable and the second binary covariate, Z, is referred to as the *confounder* variable. For example, Y might refer to the presence or absence of cancer and X might indicate whether the subject smoked or not, and Z is the presence or absence of a certain gene.

Power Calculations

Using the *logistic model*, the probability of a binary event is

$$\Pr(Y = 1|X, Z) = \frac{\exp(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ)}{1 + \exp(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ)}$$

This formula can be rearranged so that it is linear in *X* as follows

$$\log\left(\frac{\Pr(Y = 1|X, Z)}{1 - \Pr(Y = 1|X, Z)}\right) = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ$$

Note that the left side is the logarithm of the odds of a response event (Y = 1) versus a response non-event (Y = 0). This is sometimes called the *logit* transformation of the probability. In the logistic regression model, the magnitude of the relationship between interaction and the response *Y* is represented by the slope β_3.

The logistic regression model defines the baseline probability

$$P_0 = \Pr(Y = 1|X = 0, Z = 0) = \frac{\exp(\beta_0)}{1 + \exp(\beta_0)}$$

The significance of the slope β_3 is commonly tested with the Wald test

$$z = \frac{\hat{\beta}_3}{s_{\hat{\beta}_3}}$$

It is considered good practice to base the power analysis on the same test statistic that is used for analysis, so we base our power analysis on the above Wald test.

Demidenko (2008) gives the following formula for the power of the two-sided Wald test in this as

$$\text{Power} = \Phi\left(-z_{1-\frac{\alpha}{2}} + \frac{\beta_3\sqrt{N}}{\sqrt{V}}\right) + \Phi\left(-z_{1-\frac{\alpha}{2}} - \frac{\beta_3\sqrt{N}}{\sqrt{V}}\right)$$

where z is the usual quantile of the standard normal distribution and V is calculated as follows.

Let p_x be the probability that X = 1 in the sample. Similarly, let p_z be the probability that Z = 1 in the sample.

Define the relationship between X and Z as a logistic regression as follows

$$\Pr(X = 1|Z) = \frac{\exp(\gamma_0 + \gamma_1 Z)}{1 + \exp(\gamma_0 + \gamma_1 Z)}$$

The value of γ_0 is found from

$$\exp(\gamma_0) = \frac{Q + \sqrt{Q^2 + 4p_x(1 - p_x)\exp(\gamma_1)}}{2(1 - p_x)\exp(\gamma_1)}$$

$$Q = p_x\big(1 + \exp(\gamma_1)\big) + p_z\big(1 - \exp(\gamma_1)\big) - 1$$

The information matrix for this model is

$$I = \begin{bmatrix} L + F + J + R & F + R & J + R & R \\ F + R & F + R & R & R \\ J + R & R & J + R & R \\ R & R & R & R \end{bmatrix}$$

where

$$L = \frac{(1 - p_z)\exp(\beta_0)}{\big(1 + \exp(\gamma_0)\big)\big(1 + \exp(\beta_0)\big)^2}$$

$$R = \frac{p_z\exp(\beta_0 + \beta_1 + \beta_2 + \beta_3 + \gamma_0 + \gamma_1)}{\big(1 + \exp(\gamma_0 + \gamma_1)\big)\big(1 + \exp(\beta_0 + \beta_1 + \beta_2 + \beta_3)\big)^2}$$

$$F = \frac{(1 - p_z)\exp(\beta_0 + \beta_1 + \gamma_0)}{\big(1 + \exp(\gamma_0)\big)\big(1 + \exp(\beta_0 + \beta_1)\big)^2}$$

$$J = \frac{p_z\exp(\beta_0 + \beta_2)}{\big(1 + \exp(\gamma_0 + \gamma_1)\big)\big(1 + \exp(\beta_0 + \beta_2)\big)^2}$$

The value of V is the (4,4) element of the inverse of I.

The values of the regression coefficients are input as P_0, and the following odds ratio as follows

$$ORint = \exp(\beta_3)$$

$$ORyx = \exp(\beta_1)$$

$$ORyz = \exp(\beta_2)$$

$$ORxz = \exp(\gamma_1)$$

Example 1 – Sample Size for Various Odds Ratios

A study is to be undertaken to study the occurrence of a certain type of cancer (response variable), the presence of a certain food in the diet, the presence of a certain gene, and the interaction of these two covariates. The main interest is in testing the interaction.

The baseline cancer event rate is 5%. The researchers want a sample size large enough to detect an interaction odds ratio of 2, 3, and 4 with 80% power at the 0.05 significance level with a two-sided Wald test. They want to look at the sensitivity of the analysis to the specification of the ORyx, so they also want to obtain the results ORyx = 1 2 if ORyz = 1.5. They want to study the case when X and Z are independent, that is, when ORxz = 1.5. The researchers determine that about 40% of the sample eat the food being studied. They also determine that about 25% will have the gene of interest.

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**
Alternative Hypothesis ..... **Two-Sided**
Power..... **0.80**
Alpha..... **0.05**
P0 [Pr(Y=1|X=0, Z=0)] **0.05**
ORint (X,Z Interaction Odds Ratio) **2 3 4**
ORyx (Y,X Odds Ratio)..... **1 2**
ORyz (Y,Z Odds Ratio)..... **1.5**
ORxz (X,Z Odds Ratio)..... **1.5**
Percent with X = 1..... **40**
Percent with Z = 1..... **25**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Test Type: Wald Test
Variables: Y = Response, X = Exposure, Z = Confounder, Int = X and Z Interaction
Alternative Hypothesis: H1: ORint ≠ 1

Power	Sample Size N	Prevalence Percentages X = 1	Prevalence Percentages Z = 1	Baseline Probability Pr(Y = 1 | X = Z = 0) P0	Odds Ratio Interaction ORint	Odds Ratio Y, X ORyx	Odds Ratio Y, Z ORyz	Odds Ratio X, Z ORxz	Alpha
0.8001	4959	40	25	0.05	2	1	1.5	1.5	0.05
0.8001	3996	40	25	0.05	2	2	1.5	1.5	0.05
0.8002	1863	40	25	0.05	3	1	1.5	1.5	0.05
0.8002	1542	40	25	0.05	3	2	1.5	1.5	0.05
0.8000	1136	40	25	0.05	4	1	1.5	1.5	0.05
0.8004	956	40	25	0.05	4	2	1.5	1.5	0.05

Logistic Regression Equation: Log(P/(1 - P)) = β0 + β1 × X + β2 × Z + β3 × X × Z, where P = Pr(Y = 1|X, Z) and X and Z are binary.

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N	The sample size.
P0	The response probability at X = 0, Z = 0. That is, P0 = Pr(Y = 1|X = 0, Z = 0).
Percent with X = 1	The percent of the sample in which the exposure is 1.
Percent with Z = 1	The percent of the sample in which the confounder is 1.
ORint	The odds ratio of the interaction. This is the effect size. ORint = Exp(β3).
ORyx	The odds ratio of Y versus X. ORyx = Exp(β1).
ORyz	The odds ratio of Y versus Z. ORyz = Exp(β2).
ORxz	The odds ratio of X versus Z in a logistic regression of X on Z.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A two-binary-covariate logistic regression (binary response Y versus one binary X of interest and one binary confounder Z) design will be used to test whether the odds ratio for Y and the interaction of X and Z (ORint) is different from 1, given a (baseline) probability that Y equals 1 when X and Z equal 0 (P0 = Pr(Y = 1|X = Z = 0)) of 0.05 (H0: ORint = 1 versus H1: ORint ≠ 1, given P0 = 0.05). The comparison will be made using a two-sided logistic regression Wald test of β3 (using the model Log(P / (1 - P)) = β0 + β1 × X + β2 × Z + β3 × X × Z, where P = Pr(Y = 1|X, Z)), with a Type I error rate (α) of 0.05. Among subjects, 40% are assumed to have the value X = 1 (or be in the X = 1 group), and 25% are assumed to have the value Z = 1 (or be in the Z = 1 group). The odds ratio for Y and X (ORyx) is assumed to be 1, the odds ratio for Y and Z (ORyz) is assumed to be 1.5, and the odds ratio for X and Z (ORxz) is assumed to be 1.5. To detect a Y and interaction odds ratio (ORint) of 2 with 80% power, the number of needed subjects will be 4959.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	4959	6199	1240
20%	3996	4995	999
20%	1863	2329	466
20%	1542	1928	386
20%	1136	1420	284
20%	956	1195	239

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.
N The evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N' The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' 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.)
D The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 6199 subjects should be enrolled to obtain a final sample size of 4959 subjects.

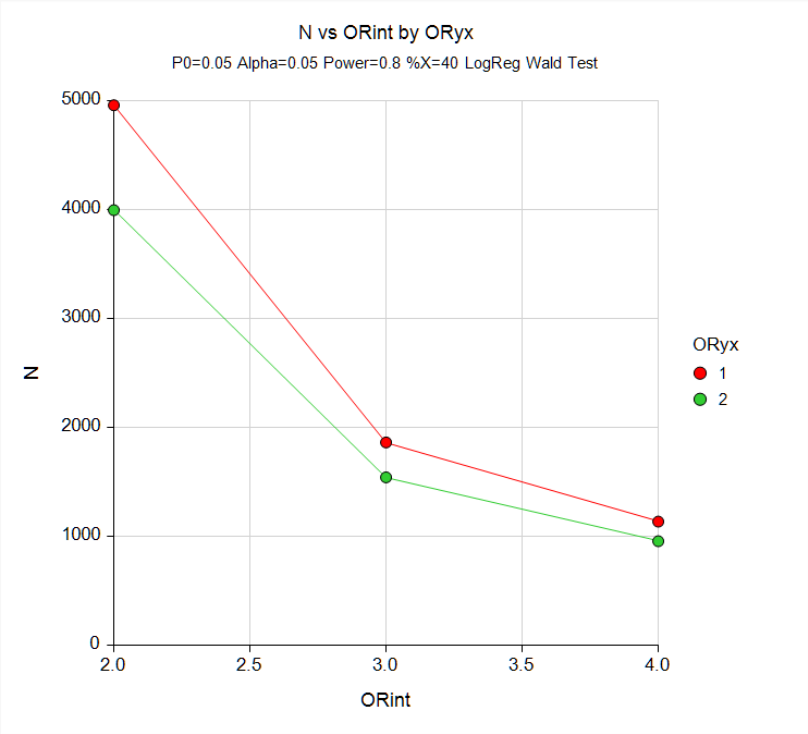
References

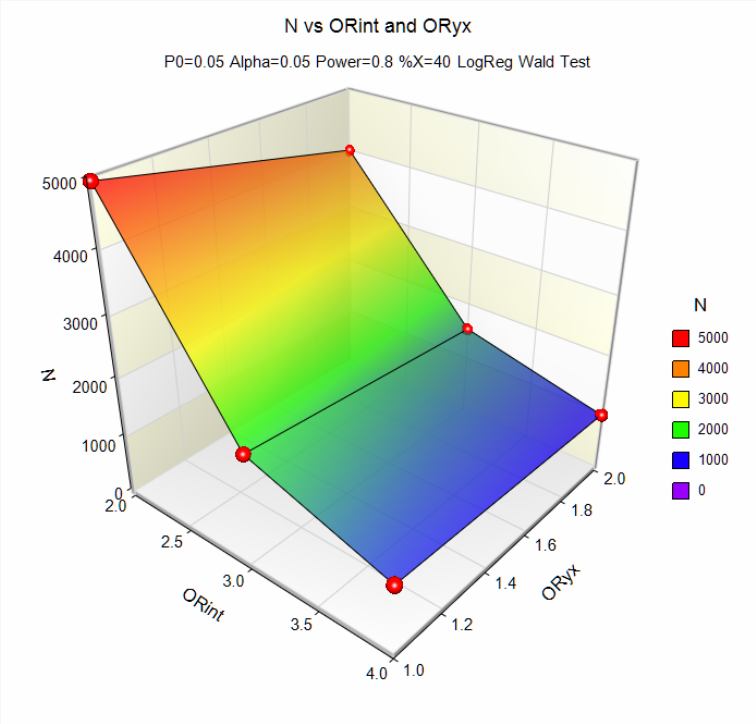
Demidenko, Eugene. 2007. 'Sample size determination for logistic regression revisited', Statistics in Medicine, Volume 26, pages 3385-3397.
Demidenko, Eugene. 2008. 'Sample size and optimal design for logistic regression with binary interaction', Statistics in Medicine, Volume 27, pages 36-46.
Rochon, James. 1989. 'The Application of the GSK Method to the Determination of Minimum Sample Sizes', Biometrics, Volume 45, pages 193-205.

This report shows the required sample size for each of the scenarios.

Plots Section

Plots





These plots show the sample size versus the odds ratio for several scenarios.

Example 2 – Validation for a Binary Covariate using Demidenko (2008)

Demidenko (2008), page 41, gives an example in which alpha = 0.05, power = 0.8, ORyx = 1, ORyz= 1, ORxz = 1, P0 = 0.5, percent X = 1 is 40, and percent Z = 1 is 25. For ORint = 2, 3, 4, 5, and 10, N = 1534, 665, 455, 366, and 252. Because the article only gives a graph which allows only approximate values, we calculated the exact values using Demidenko's website: www.dartmouth.edu/~eugened/power-samplesize.php. We will validate this routine by running the same problem.

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**
Alternative Hypothesis ..... **Two-Sided**
Power..... **0.80**
Alpha..... **0.05**
P0 [Pr(Y=1|X=0, Z=0)] **0.5**
ORint (X Z Interaction Odds Ratio) **2 3 4 5 10**
ORyx (Y,X Odds Ratio)..... **1**
ORyz (Y,Z Odds Ratio)..... **1**
ORxz (X,Z Odds Ratio)..... **1**
Percent with X = 1..... **40**
Percent with Z = 1..... **25**

Output

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

Numeric Results

Solve For: Sample Size
Test Type: Wald Test
Variables: Y = Response, X = Exposure, Z = Confounder, Int = X and Z Interaction
Alternative Hypothesis: H1: ORint ≠ 1

Power	Sample Size N	Prevalence Percentages X = 1	Prevalence Percentages Z = 1	Baseline Probability Pr(Y = 1 | X = Z = 0) P0	Odds Ratio Interaction ORint	Odds Ratio Y, X ORyx	Odds Ratio Y, Z ORyz	Odds Ratio X, Z ORxz	Alpha
0.8001	1534	40	25	0.5	2	1	1	1	0.05
0.8001	665	40	25	0.5	3	1	1	1	0.05
0.8001	455	40	25	0.5	4	1	1	1	0.05
0.8007	367	40	25	0.5	5	1	1	1	0.05
0.8008	252	40	25	0.5	10	1	1	1	0.05

Logistic Regression Equation: Log(P/(1 - P)) = β0 + β1 × X + β2 × Z + β3 × X × Z, where P = Pr(Y = 1|X, Z) and X and Z are binary.

PASS matches Demidenko's results except for ORint = 5. In this case N = 367 was required to achieve at least 0.8 power as specified.