

Chapter 128

Tests for the Ratio of Two Means (Normal Data)

Introduction

This procedure calculates power and sample size for t-tests and z-tests from a parallel-groups design with two groups when the data are assumed to follow the normal distribution (so the log transformation is not used). This routine deals with the case in which the statistical hypotheses are expressed in terms of mean ratios instead of mean differences.

The details of this analysis are given in Rothmann, Wiens, and Chan (2012) and, to lesser extent, in Kieser and Hauschke (1999).

Note that when the data follow a log-normal distribution rather than the normal distribution so that a log transformation is used, you should use another PASS procedure entitled *Tests for the Ratio of Two Means (Log-Normal Data)* to obtain more accurate results.

Testing Using Ratios

It will be convenient to adopt the following specialized notation for the discussion of these tests.

<u>Parameter</u>	<u>PASS Input/Output</u>	<u>Interpretation</u>
μ_1	Not used	<i>Group 1 mean.</i> This is the treatment mean.
μ_2	Not used	<i>Group 2 mean.</i> This is the control mean.
R_0	R0	<i>Null ratio.</i> This is the value of $R = \mu_1/\mu_2$ under the null hypothesis, H_0 .
R	R1	<i>Actual ratio.</i> This is the value of $R = \mu_1/\mu_2$ at which the power is calculated.

Note that the actual values of μ_1 and μ_2 are not needed. Only the ratio of these values is needed for power and sample size calculations.

In the two-sided case, the null and alternative hypotheses are

$$H_0: R = R_0 \quad \text{versus} \quad H_1: R \neq R_0.$$

The one-sided hypotheses are

$$H_0: R \leq R_0 \quad \text{versus} \quad H_1: R > R_0$$

and

$$H_0: R \geq R_0 \quad \text{versus} \quad H_1: R < R_0.$$

Coefficient of Variation

The coefficient of variation (CV) is the ratio of the standard deviation to the mean of group 2, the control group. This parameter is used to represent the variation in the data. That is, $CV = \frac{\sigma_2}{\mu_2}$.

Power Calculation

We will use three of the four tests are provided by Rothmann, Wiens, and Chan (2012) for testing the mean ratio directly when the data are assumed to be normally distributed (untransformed). This section will summarize these tests and the associated power and sample size formulas. Rothmann, Wiens, and Chan (2012) provide a much more complete discussion of this topic.

Tests

This section will provide technical details about the three available test statistics that are available. We begin with some nomenclature.

Suppose a comparison is to be made between two groups labelled “1” and “2”. When desired, you can think of group 1 as the treatment group and group 2 as the control group. The response of interest is assumed to follow the normal distribution with (possibly different) means μ_1 and μ_2 and variances σ_1^2 and σ_2^2 . To conduct the comparison, a random sample of N_1 and N_2 subjects will be obtained for each group. The parameters of the study are presented in terms of the mean ratio $R = \mu_1/\mu_2$.

In the results below, let $\lambda = \sigma_1/\sigma_2$, $k = N_1/N_2$, $CV = \sigma_2/\mu_2$, and β be the probability of a type II error.

The three test statistics are (1) an equal variance t-test, (2) unequal variances large sample z-test, and (3) unequal variances Satterthwaite t-test.

Equal Variances T-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0: \frac{\mu_1}{\mu_2} = R_0 \text{ versus } H_1: \mu_1/\mu_2 \neq R_0$$

to

$$H_0: \mu_1 - R_0\mu_2 = 0 \text{ versus } H_1: \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_1 = \frac{\bar{X}_1 - R_0\bar{X}_2}{\sqrt{S \left(\frac{1}{N_1} + \frac{R_0^2}{N_2} \right)}}$$

where \bar{X}_1 and \bar{X}_2 are the sample means of the two groups and S is the pooled estimate of the standard deviation, σ which is given by

$$S^2 = \frac{(N_1 - 1)s_1^2 + (N_2 - 1)s_2^2}{N_1 + N_2 - 2}$$

It is assumed that T_1 is distributed as a central t distribution with degrees of freedom given by $N_1 + N_2 - 2$.

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For a specified alternative $R = R_1$, T_1 follows the noncentral t distribution with $N_1 + N_2 - 2$ degrees of freedom and noncentrality

$$\left(\frac{R - R_0}{CV}\right) \sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr(T_1 \geq t_{1-\alpha/2, N_1+N_2-2} | R, R_0, CV)$$

Unequal Variances Large Sample Z-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0: \frac{\mu_1}{\mu_2} = R_0 \text{ versus } H_1: \mu_1/\mu_2 \neq R_0$$

to

$$H_0: \mu_1 - R_0\mu_2 = 0 \text{ versus } H_1: \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_2 = \frac{\bar{x}_1 - R_0\bar{x}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

where \bar{x}_1 and \bar{x}_2 are the sample means of the two groups and s_1 and s_2 are the estimated of the standard deviations.

It is assumed that T_2 has a standard normal distribution when the null hypothesis is true. When $|T_2| > z_{1-\alpha/2}$, the null hypothesis is rejected, and inequality is concluded at a two-sided level of α .

Hence, the approximate power of this test is given by

$$z_\beta = \frac{\mu_1 - R_0\mu_2}{\sqrt{\frac{\sigma_1^2}{N_1} + R_0^2 \frac{\sigma_2^2}{N_2}}} - z_{\alpha/2}$$

This can be rearranged to give

$$z_\beta = \sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}} \left(\frac{R - R_0}{CV}\right) - z_{\alpha/2}$$

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Unequal Variances Satterthwaite T-Test

The two-sided, ratio hypotheses are rearranged as from

$$H_0: \frac{\mu_1}{\mu_2} = R_0 \text{ versus } H_1: \mu_1/\mu_2 \neq R_0$$

to

$$H_0: \mu_1 - R_0\mu_2 = 0 \text{ versus } H_1: \mu_1 - R_0\mu_2 \neq 0$$

The null hypothesis is tested using the test statistic

$$T_3 = \frac{\bar{x}_1 - R_0\bar{x}_2}{\sqrt{\frac{\sigma_1^2}{N_1} + R_0^2 \frac{\sigma_2^2}{N_2}}}$$

where \bar{x}_1 and \bar{x}_2 are the sample means of the two groups and s_1 and s_2 are the estimated of the standard deviations.

It is assumed that the distribution of T_3 is a Satterthwaite adjusted central t instead of a standard normal when the null hypothesis is true. When $|T_3| > t_{1-\alpha/2, \nu}$, the null hypothesis is rejected, and inequality is concluded at a two-sided level of α . The Satterthwaite degrees of freedom is given by

$$\nu = \frac{\left[\frac{s_1^2}{N_1} + R_0^2 \frac{s_2^2}{N_2} \right]^2}{\frac{s_1^4}{N_1(N_1 - 1)} + R_0^4 \frac{s_2^4}{N_2(N_2 - 1)}}$$

The power of this test is given by the non-central t distribution with degrees of freedom ν' estimated by substituting the standard deviations σ_1 and σ_2 for s_1 and s_2 in the formula for ν . The resulting value of ν' is

$$\nu' = \frac{\left[R^2 + \frac{\lambda^2}{k} \right]^2}{\frac{\lambda^4}{k^2(kN_2 - 1)} + \frac{R_0^4}{N_2 - 1}}$$

The non-centrality parameter is given by

$$\left(\frac{R - R_0}{CV} \right) \sqrt{\frac{N_2}{\frac{\lambda^2}{k} + R_0^2}}$$

Hence, the power of this test is given by

$$(1 - \beta) = Pr(|T_2| \geq t_{1-\alpha/2, \nu'} | R, R_0, CV)$$

Example 1 – Finding Sample Size

A company has developed a generic drug for treating rheumatism and wants to show that it is different from the standard drug. Responses are thought to follow a normal distribution with unequal variances. A parallel-group design will be used, and the data will be analyzed with a Satterthwaite corrected, two-sample t-test.

Researchers have decided to set $R_0 = 1$, $R_1 = 0.7, 0.8, \text{ or } 0.9$. Past experience leads the researchers to set the CV to 1. The significance level is 0.05 and the power is 0.9. The ratio of the two standard deviations is assumed to be 0.5 or 1.0.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Alternative Hypothesis	Two-Sided (H1: $R \neq R_0$)
Test Type	Unequal Variances Satterthwaite T-Test
Power	0.90
Alpha	0.05
Group Allocation	Equal (N1 = N2)
R0 (Ratio H0)	1.0
R1 (Ratio H1)	0.7 0.8 0.9
CV (Coef of Variation, σ_2 / μ_2)	1
λ (Ratio of σ 's, σ_1 / σ_2)	0.5 1

Annotated Output

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

Numeric Results

Numeric Results

Ratio (R): μ_1 / μ_2
 Hypotheses: $H_0: R = R_0$ vs. $H_1: R \neq R_0$
 Test: Unequal Variances Satterthwaite T-Test

Target Power	Actual Power	N1	N2	N	Ratio of Means		Coef of Variation Control CV	Ratio of σ 's λ	Alpha
					Ratio H0 R0	Ratio H1 R1			
0.9	0.90146	148	148	296	1	0.7	1	0.5	0.05
0.9	0.90065	235	235	470	1	0.7	1	1.0	0.05
0.9	0.90029	330	330	660	1	0.8	1	0.5	0.05
0.9	0.90022	526	526	1052	1	0.8	1	1.0	0.05
0.9	0.90006	1314	1314	2628	1	0.9	1	0.5	0.05
0.9	0.90004	2102	2102	4204	1	0.9	1	1.0	0.05

References

Rothmann, M.D., Wiens, B.L., and Chan, I.S.F. 2012. Design and Analysis of Non-Inferiority Trials. Taylor & Francis/CRC Press. Boca Raton, Florida.

Kieser, M. and Hauschke, D. 1999. 'Approximate Sample Sizes for Testing Hypotheses about the Ratio and Difference of Two Means.' Journal of Biopharmaceutical Studies, Volume 9, No. 4, pages 641-650.

Hauschke, D., Kieser, M., Diletti, E., Burke, M. 1999. 'Sample Size Determination for Proving Equivalence Based on the Ratio of Two Means for Normally Distributed Data.' Statistics in Medicine, Volume 18, pages 93-105.

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Report Definitions

Target Power is the desired power value (or values) entered in the procedure. Power is the probability of rejecting a false null hypothesis.
 Actual Power is the power obtained in this scenario. Because N1 and N2 are discrete, this value is often (slightly) larger than the target power.
 N1 is the number of subjects sampled from the treatment population.
 N2 is the number of subjects sampled from the control population.
 N is the total sample size, N1 + N2.
 R0 is the ratio of means (μ_1/μ_2) assumed by the null hypothesis.
 R1 is the ratio of means (μ_1/μ_2) assumed by the alternative hypothesis.
 CV is the coefficient of variation of group 2, the control group. $CV = \sigma_2 / \mu_2$.
 λ is the ratio of the standard deviations of groups 1 and 2. $\lambda = \sigma_1 / \sigma_2$.
 Alpha is the probability of rejecting a true null hypothesis.

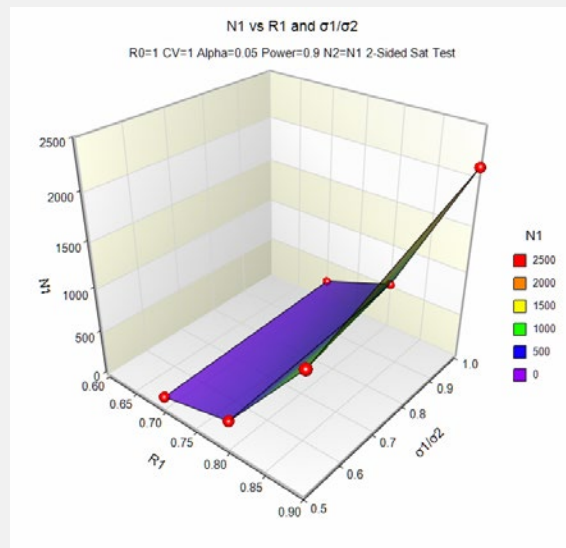
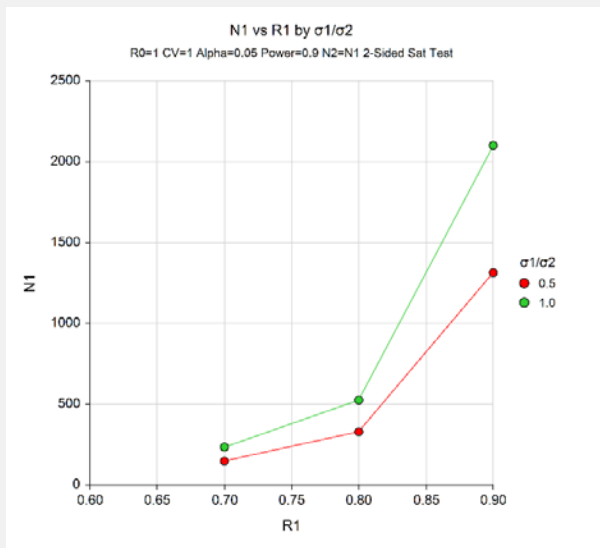
Summary Statements

Group sample sizes of 148 in group 1 and 148 in group 2 achieve 90% power using a two-sided, unequal variances Satterthwaite t-test, which is computed from the original, untransformed, data. The significance level (alpha) of the test is 0.05. The data are assumed to be normally distributed. The ratio of the means under the null hypothesis is 1. The ratio of the means at which the power is evaluated is 0.7. The coefficient of variation of the control group is 1. The ratio of the group standard deviations, σ_1 / σ_2 , is 0.5.

This report shows the sample size required for the indicated scenarios.

Chart Section

Chart Section



These plots show the sample size for the various scenarios.

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Example 2 – Validation using Rothmann et al. (2012)

Rothmann *et al.* (2012) present a table on page 342 in which they calculate several sample sizes. Specifically, they calculate the sample size for the large sample z-test to be 20 in each group for a one-sided test.

The R0 is 0.75, R1 is 0.95, CV is 0.3, alpha is 0.025, power is 0.9, and SD ratio is 0.5.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Alternative Hypothesis	One-Sided (H1: R > R0)
Test Type	Unequal Variances Large Sample Z-Test
Power	0.90
Alpha	0.025
Group Allocation	Equal (N1 = N2)
R0 (Ratio H0)	0.75
R1 (Ratio H1)	0.95
CV (Coef of Variation, σ_2 / μ_2)	0.3
λ (Ratio of σ 's, σ_1 / σ_2)	0.5

Output

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

Numeric Results

Numeric Results									
Ratio (R): μ_1 / μ_2									
Hypotheses: H0: R \leq R0 vs. H1: R > R0									
Test: Unequal Variances Large Sample Z-Test									
Target Power	Actual Power	N1	N2	N	Ratio of Means		Coef of Variation Control CV	Ratio of σ 's λ	Alpha
					Ratio H0 R0	Ratio H1 R1			
0.9	0.91111	20	20	40	0.75	0.95	0.3	0.5	0.025

PASS also calculates the sample size in each group to be 20. Thus, the procedure is validated.