Chapter 647

Meta-Analysis of Tests for the Risk Ratio of Two Proportions using a Fixed-Effects Model in a Cluster-Randomized Design

Introduction

This procedure calculates power and number of studies for fixed-effect meta-analyses of cluster-randomized, two-group studies that are summarized by the risk ratios of two group proportions.

Meta-Analysis

Meta-analysis refers to the systematic assessment of a group of two or more individual studies (experiments or clinical trials). The studies must be similar so that their results may be numerically compared. For example, in this procedure all studies must have as their outcome two group proportions whose risk ratio is used to compare their values.

By combining the results of several studies, their individual results may be summarized and assessed. The power of the combined test will be increased since it represents a larger sample.

Fixed-Effects versus Random-Effects Models

The *fixed-effects model*, which is assumed in this procedure, assumes that all studies have the same true effect size. That is, it assumes that all factors that might influence the effect size are the same so that the true effect size for all studies is the same. Therefore, only the *within study variability* needs to be considered since the effect size variation occurs because of random error.

The *random-effects model*, which is assumed in another procedure, assumes that the studies in the analysis are similar, but not to the extent that they all have the same true effect size. Instead, it is assumed that each study has its own true effect size and that the particular outcome of the study is a sample from a distribution with that proportion. The random-effects model must not only account for the *within study variability*, but it must also account for the *between study variability*.

Technical Details

The Meta-Analysis of the Risk Ratio of Two Proportions

The power formulas used by this procedure are an adaptation of those given in Harrer *et al.* (2022), Campbell and Walters (2014), Ahn, Heo, and Zhang (2015), Donner and Klar (2002), Donner, Piaggio, and Villar (2003), and Eldridge and Kerry (2012) page 204.

Cluster-randomized designs are those in which whole clusters of subjects (classes, hospitals, communities, etc.) are randomized into a treatment group or a control group. It is assumed that each study resulted in two group proportions, made up of K_i clusters of M_{ij} subjects each, and was analyzed using summary statistics created from the individual subject data. The sample sizes for each study were adjusted to compensate for the cluster-randomization using a *design effect* (DE) factor.

A series of H studies are assumed to each have an effect size of RR which is the risk ratio of two group proportions. The results of these individual studies may be combined into one overall statistical test that draws a more precise conclusion.

Test Statistic

Suppose each study has two populations from which dichotomous (binary) responses are recorded. The probability (or risk) of obtaining the event of interest in population 1 (the treatment group) is p_1 and in population 2 (the control group) is p_2. The corresponding failure proportions are given by $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$.

An 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 the group and that the response from one subject is independent of that of any other subject.

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

Group	Success	Failure	Total
Treatment	*a*	*c*	*m*
Control	*b*	*d*	*n*
Total	*s*	*f*	*N*

The following alternative notation is sometimes used.

Group	Success	Failure	Total
Treatment	x_{11}	x_{12}	n_1
Control	x_{21}	x_{22}	n_2
Total	m_1	m_2	N

The binomial proportions, p_1 and p_2, are estimated from these data using the formulae

$$\hat{p}_1 = \frac{a}{m} = \frac{x_{11}}{n_1} \quad \text{and} \quad \hat{p}_2 = \frac{b}{n} = \frac{x_{21}}{n_2}$$

Risk Ratio

The risk ratio is computed as

$$RR = \frac{p_1}{p_2}$$

Meta-Analysis for the Risk Ratio of Proportions

Suppose the individual tables are summarized into one 2-by-2 table whose individual cells now contain the corresponding cell averages which are still named *a*, *b*, *c*, and *d*. These counts can be reparametrized using the two group proportions *P*1 and *P*2 and the two average-group sample sizes *N*1 and *N*2.

These sample sizes are obtained from the cluster-randomized design parameters *K*1, *M*1, *K*2, and *M*2 using the formulas

$$Ni = \frac{Ki(Mi)}{DE_i}, i = 1,2$$

where

$$DE_1 = 1 + \big((COV^2 + 1)M_1 - 1\big)\rho$$

$$DE_2 = 1 + \big((COV^2 + 1)M_2 - 1\big)\rho$$

These are called the *effective* sample sizes. These adjusted sample sizes can then be used in the regular, two-group formulas given next. The average cell counts are

$$a = (P1)(N1)$$
$$b = (P2)(N2)$$
$$c = (1 - P1)(N1)$$
$$d = (1 - P2)(N2)$$

Using these summary statistics, a summary effect size called the *log risk ratio* can be calculated using

$$\log(RR) = \log\left(\frac{P1}{P2}\right)$$

along with an estimate of its standard error

$$SE_{\log RR} = \sqrt{\frac{1}{H}\left(\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}\right)}$$

Using a fixed-effect model, these results may be summarized and tested using the meta-analysis z-test as

$$Z = \frac{\log(RR) - \log(RR_0)}{SE_{\log RR}}$$

We assume that Z follows the standard normal distribution and so it can be used to test the null hypothesis $H_0: RR = RR_0$ at significance level of α.

Hypotheses

Three statistical hypotheses commonly used are

$$H_0: RR \leq RR_0 \quad \text{vs.} \quad H_1: RR > RR_0$$

$$H_0: RR \geq RR_0 \quad \text{vs.} \quad H_1: RR < RR_0$$

$$H_0: RR = RR_0 \quad \text{vs.} \quad H_1: RR \neq RR_0$$

Power Calculation

The power of a one-tailed test that $RR = RR_0$ is given by

$$Power = 1 - \Phi(c_\alpha - \lambda)$$

where OR is set by the alternative hypothesis, c_α is the $1 - \alpha$ quantile of the standard normal distribution, and

$$\lambda = \frac{\log(RR) - \log(RR_0)}{SE_{\log RR}}$$

The power of a two-tailed test that $RR = RR_0$ is given by

$$Power = 1 - \Phi(c_{\alpha/2} - \lambda) + \Phi(-c_{\alpha/2} - \lambda)$$

These formulas can be used in search algorithms to determine the necessary number of studies required to achieve a desired level of power.

Note that the values of P1.0 (P1 assuming H0) and P1.1 (P1 assuming H1) can be obtained from the risk ratios using

$$P1.0 = RR_0 P2$$

and

$$P1.1 = RR_1(P2)$$

where RR_1 is the risk ratio at which the power is calculated.

Example 1 – Finding the Number of Studies

Researchers wish to determine a reasonable number of studies for a meta-analysis with the following characteristics: two-group, equal-allocation trials, two-sided significance level of 0.05, power of 0.9, $P2 = 0.5$, $RR_1 = 1.1, 1.25, 1.5$, and $RR_0 = 1.0$. The average number of clusters per study in both groups is 7. The average size of each cluster is 8. The coefficient of variation of cluster sizes is 0.65. The intracluster correlation is 0.05.

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 ....**Number of Studies**
Alternative Hypothesis ....**Two-Sided (H1: RR ≠ RR0)**
Power..**0.90**
Alpha..**0.05**
K1 (Average Number of Clusters).................**7**
M1 (Average Cluster Size)............................**8**
K2 (Average Number of Clusters).................**K1**
M2 (Average Cluster Size)............................**M1**
COV of Cluster Sizes....................................**0.65**
RR0 (Risk Ratio|H0) **1.0**
RR1 (Risk Ratio|H1) **1.1 1.25 1.5**
P2 (Group 2 Proportion)...............................**0.5**
ρ (Intracluster Correlation, ICC)....................**0.05**

Output

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

Numeric Reports

Numeric Results
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Solve For: Number of Studies
Hypotheses: H0: RR = RR0 vs. H1: RR ≠ RR0
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Power	Number of Studies H	Number of Clusters		Cluster Size		Sample Size		Risk Ratio		Proportion			
		Average K	Total HK	Average M	COV	Average N	Total HN	RR|H1 RR1	RR|H0 RR0	P|H1 P.1	P|H0 P.0	ICC ρ	Alpha
0.90062	64	14	896			112	7168	1.10	1				0.05
[Group 1]		7	448	8	0.65	56	3584			0.550	0.5	0.05	
[Group 2]		7	448	8	0.65	56	3584			0.500	0.5	0.05	
0.90452	13	14	182			112	1456	1.25	1				0.05
[Group 1]		7	91	8	0.65	56	728			0.625	0.5	0.05	
[Group 2]		7	91	8	0.65	56	728			0.500	0.5	0.05	
0.92090	6	14	84			112	672	1.50	1				0.05
[Group 1]		7	42	8	0.65	56	336			0.750	0.5	0.05	
[Group 2]		7	42	8	0.65	56	336			0.500	0.5	0.05	
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Power   The probability of rejecting a false null hypothesis about the risk ratio. This is the power calculated at the actual risk ratio.

[Group]   The group to which the results on this line belong. Group 1 is the treatment group and group 2 is the control group. The first line shows the settings that are used for both groups.

H   The number of studies included in the meta-analysis.

K   The average number of clusters per study. These clusters are split between groups 1 and 2. The average cluster count in each group is shown below on the next two lines.

HK   The total number of clusters in the meta-analysis. These clusters are split between groups 1 and 2. The total cluster counts for each group are given below on the next two lines.

M   The average cluster size (i.e., number of subjects per cluster) in groups 1 and 2.

COV   The coefficient of variation of the cluster sizes of the clusters within the group. This value is used for both groups.

N   The average number of subjects per study. The total sample size is shown as the top row followed by N1 and N2.

HN   The total number of subjects represented in the meta-analysis. HN = H x N. The subtotals for groups 1 and 2 are shown below.

RR1   The value of the risk ratio assumed by the alternative hypothesis, H1. This is the risk ratio at which the power is calculated.

RR0   The value of the risk ratio assumed by the null hypothesis, H0.

P.1   The value of the response proportion of groups 1 and 2 assumed by the alternative hypothesis, H1.

P.0   The value of the response proportion of groups 1 and 2 assumed by the null hypothesis, H0.

ρ   The intracluster correlation (ICC) between any two observations from within a cluster. This statistic has two common interpretations: (1) the proportion of variation related to the between-cluster variation or (2) the correlation between two subjects from the same cluster.

Alpha   The probability of rejecting a true null hypothesis.

Summary Statements
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A collection of two-group cluster-randomized-design studies will be used to test whether the Group 1 proportion is different from the Group 2 proportion (H0: RR = 1 versus H1: RR ≠ 1, RR = P1 / P2). The meta-analysis comparison will be made using a two-sided fixed-effects-model Z-test, with a Type I error rate (α) of 0.05. In Group 1, the studies are assumed to have an average of 7 clusters with an average of 8 subjects per cluster (totaling 56 subjects), and in Group 2, an average of 7 clusters with an average of 8 subjects per cluster (totaling 56 subjects). The coefficient of variation of the cluster sizes within a group is assumed to be 0.65. The intracluster correlation coefficient of responses within a cluster is assumed to be 0.05. The response proportion of Group 2 (the control group) is assumed to be 0.5. To detect a risk ratio (RR) of 1.1 with 90% power, the number of needed studies will be 64.
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References
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Valentine, J.C., Pigott, T.D., and Rothstein, H.R. 2010. 'How Many Studies Do You Need? A Primer on Statistical
    Power for Meta-Analysis', Journal of Education and Behavioral Statistics, Volume 35, No. 2, pages 215-247.
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This report shows the sample sizes for the indicated scenarios.

Plots Section

Plots
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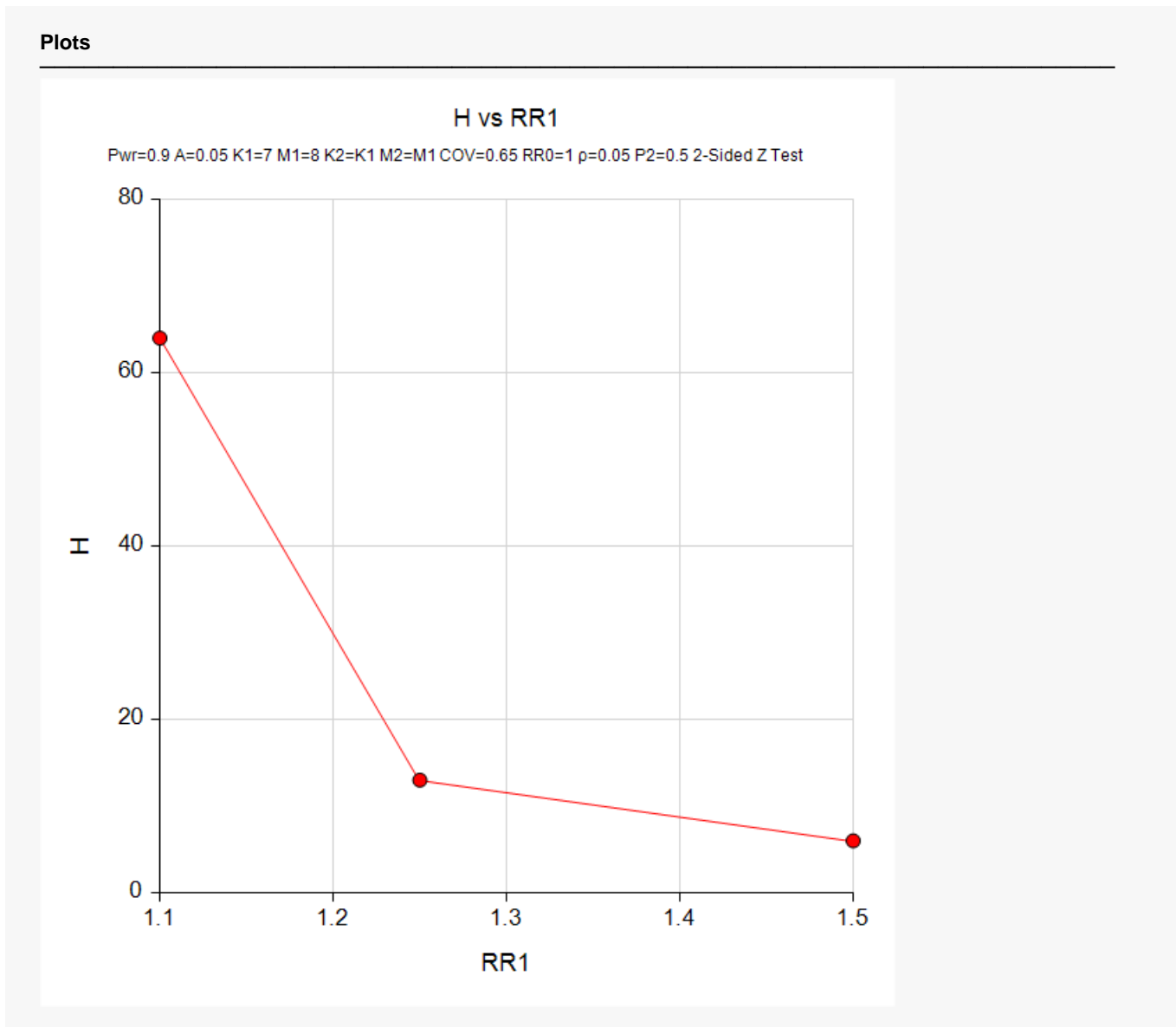
This plot represents the required number of studies for various values of RR1.

Example 2 – Validation using Hand Calculations

We could not find a validation example for this procedure in the literature so we will validate the procedure using hand calculations.

Suppose a meta-analysis is contemplated with the following characteristics: two-group, equal-allocation trials, two-sided significance level of 0.05 number of studies = 9, average cluster size of all studies is 15, average number of clusters = 10, COV = 0.65, $\rho = 0.04, P2 = 0.5, RR_1 = 1.2$, and $RR_0 = 1.0$. Calculate the power.

First, we will calculate the power directly using the formulas given above.

Step 1: Find the effective sample sizes.

To do this, first calculate the value of DE. The formula for DE is

$$DE = 1 + \{[COV^2 + 1]\bar{M} - 1\}\rho$$

Plugging in *COV* = 0.65, *M* = 15, and ρ = 0.04 gives

$$DE = 1 + \{[0.65^2 + 1]15 - 1\}(0.04) = 1.8135$$

The effective sample sizes are then found as follows.

$$N1 = N2 = \frac{10(15)}{1.8135} = 82.713$$

Step 2: Compute the value of *P*1.

$$P1 = (RR1)P2 = (1.2)0.5 = 0.6$$

Step 3: Compute the average cell counts.

$$a = (P1)(N1) = 0.6(82.713) = 49.6278$$
$$b = (P2)(N2) = 0.5(82.713) = 41.3565$$
$$c = (1 - P1)(N1) = 0.4(82.713) = 33.0852$$
$$d = (1 - P2)(N2) = 0.5(82.713) = 41.3565$$

Step 4: Compute the effect size.

$$\log(RR1) = \log(1.2) = 0.1823216$$

Step 5: Compute the within-study variance component.

$$V_W = \frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}$$

$$= \frac{1}{49.6278} + \frac{1}{33.0852} - \frac{1}{49.6278 + 41.3565} - \frac{1}{33.0852 + 41.3565}$$

$$= 0.0259508$$

Step 6: Compute the standard error of the effect size.

$$SE_{\log RR} = \sqrt{\frac{V_W}{H}} = \sqrt{\frac{0.0259508}{9}} = 0.0536975$$

Step 7: Compute λ.

$$\lambda = \frac{\log(RR) - \log(RR_0)}{SE_{\log RR}} = \frac{0.1823216 - 0}{0.0536975} = 3.3953480$$

Step 8: Compute $c_{\alpha/2}$.

$$c_{\alpha/2} = \Phi(1 - 0.025) = 1.95996398$$

Step 9: Compute the power.

$$
\begin{aligned}
Power &= 1 - \Phi(c_{\alpha/2} - \lambda) + \Phi(-c_{\alpha/2} - \lambda) \\
&= 1 - \Phi(1.95996398 - 4.0805429) + \Phi(-1.95996398 - 4.0805429) \\
&= 1 - \Phi(-1.4353840) + \Phi(-5.355312) \\
&= 1 - 0.07558852 + 0.000000 \\
&= 0.92441148
\end{aligned}
$$

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	**Power**
Alternative Hypothesis	**Two-Sided (H1: RR ≠ RR0)**
Alpha...	**0.05**
H (Number of Studies)	**9**
K1 (Average Number of Clusters)..................	**10**
M1 (Average Cluster Size)............................	**15**
K2 (Average Number of Clusters).................	**K1**
M2 (Average Cluster Size)............................	**M1**
COV of Cluster Sizes....................................	**0.65**
RR0 (Risk Ratio|H0)	**1.0**
RR1 (Risk Ratio|H1)	**1.2**
P2 (Group 2 Proportion)................................	**0.5**
ρ (Intracluster Correlation, ICC)....................	**0.04**

Output

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

Numeric Results

Solve For: Power
Hypotheses: H0: RR = RR0   vs.   H1: RR ≠ RR0

Power	Number of Studies H	Number of Clusters		Cluster Size		Sample Size		Risk Ratio		Proportion			
		Average K	Total HK	Average M	COV	Average N	Total HN	RR|H1 RR1	RR|H0 RR0	P|H1 P.1	P|H0 P.0	ICC ρ	Alpha
0.92441	9	20	180			300	2700	1.2	1				0.05
[Group 1]		10	90	15	0.65	150	1350			0.6	0.5	0.04	
[Group 2]		10	90	15	0.65	150	1350			0.5	0.5	0.04	

PASS also calculates a power of 0.92441 which validates the procedure.