Chapter 457

Meta-Analysis of Correlated Proportions

Introduction

This module performs a meta-analysis of a set of correlated, binary-event studies. These studies usually come from a design in which two dichotomous responses are made on each subject (or subject pair). The results of each study can be summarized as counts in a 2-by-2 table. For example, the binary response is recorded after treatment A and again after treatment B. The response is '1' if the event of interest occurs or '0' otherwise. This analysis also applies to *matched pairs* data in which each *case* subject is matched with a similar subject from a *control* group.

The program provides a complete set of numeric reports and plots to allow the investigation and presentation of the studies. The plots include the *forest plot, radial plot,* and *L'Abbe plot.* Both fixed- and random-effects models are available for analysis.

Meta-Analysis refers to methods for the systematic review of a set of individual studies with the aim to combine their results. Meta-analysis has become popular for a number of reasons:

1. The adoption of evidence-based medicine, which requires that all reliable information is considered.

2. The desire to avoid narrative reviews which are often misleading.

3. The desire to interpret the large number of studies that may have been conducted about a specific treatment.

4. The desire to increase the statistical power of the results by combining many small-size studies.

The goals of meta-analysis may be summarized as follows. A meta-analysis seeks to systematically review all pertinent evidence, provide quantitative summaries, integrate results across studies, and provide an overall interpretation of these studies.

We have found many books and articles on meta-analysis. In this chapter, we briefly summarize the information in Sutton et al (2000) and Thompson (1998). Refer to those sources for more details about how to conduct a meta-analysis.

Treatment Effects

Suppose you have obtained the results for *k* studies, labeled *i = 1, …, k*. Each study consists of two dichotomous measurements Y_1 and Y_2 on each of *n* subjects (the 'subject' may be a pair of matched individuals). Measurement Y_1 represents the treatment response and Y_2 represents the control response. The results of each study are summarized by four counts:

a_i the number of $Y_1 = 1$ and $Y_2 = 1$.

b_i the number of $Y_1 = 1$ and $Y_2 = 0$.

c_i the number of $Y_1 = 0$ and $Y_2 = 1$.

d_i the number of $Y_1 = 0$ and $Y_2 = 0$.

Occasionally, one of these counts will be zero which causes calculation problems. To avoid this, the common procedure is to add a small value of 0.5 or 0.25 to all counts so that zero counts do not occur.

Odds Ratio

When a paired design is used, Sahai and Khurshid (1995) indicate that the odds ratio is estimated using the following simple formula of McNemar which is based on the Mantel-Haenszel estimator.

$$OR_i = \frac{b_i}{c_i}$$

For statistical analysis, the logarithm of the odds ratio is usually used because its distribution is more accurately approximated by the normal distribution for smaller sample sizes. Sahai and Khurshid (1995) page 119 give the variance of the sample log odds ratio is estimated by

$$\hat{V}(\ln(OR_i)) = \frac{1}{b_i} + \frac{1}{c_i}$$

Risk Ratio or Relative Risk

Following Sahai and Khurshid (1995) page 139, the risk ratio is estimated as follows.

$$RR_i = \frac{a_i + b_i}{a_i + c_i}$$

Like the odds ratio, the logarithm of the risk ratio is used because its distribution is more accurately approximated by the normal distribution for smaller sample sizes. The variance of the sample log risk ratio is estimated by

$$\hat{V}(\ln(RR_i)) = \frac{(b_i + c_i)}{(a_i + c_i)(a_i + b_i)}$$

Risk Difference

Following Sahai and Khurshid (1995) page 139, the risk difference is calculated as follows.

$$RD_i = \frac{b_i - c_i}{n_i}$$

The estimated variance of the sample risk difference is given by

$$\hat{V}(RD_i) = \frac{n_i(b_i + c_i) - (b_i - c_i)^2}{n_i^3}$$

Defining the Study Parameters

Let θ_i represent the outcome measure created from the 2-by-2 table. That is, θ_i may be the odds ratio, risk ratio, or risk difference. Let $\hat{\theta}_i$ represent the estimate of θ_i from the study. Confidence intervals based on the normal distribution may be defined for θ_i in the usual manner.

$$\hat{\theta}_i \pm z_{1-\alpha/2}\sqrt{\hat{V}(\hat{\theta}_i)}$$

In the case of the odds ratio and the risk ratio, the interval is created on the logarithmic scale and then transformed back to the original scale.

It will be useful in the sequel to make the following definition of the weights.

$$v_i = \hat{V}(\hat{\theta}_i)$$

$$w_i = 1 \,/\, v_i$$

Hypothesis Tests

Several hypothesis tests have been developed to test the various hypotheses that may be of interest. These will be defined next.

Overall Null Hypothesis

Two statistical tests have been devised to test the overall null hypothesis that all treatment effects are zero. The null hypothesis is written

$$H_0 : \theta_i = 0 \quad i = 1, \cdots, k$$

Nondirectional Test

The nondirectional alternative hypothesis that at least one $\theta_i \neq 0$ may be tested by comparing the quantity

$$X_{ND} = \sum_{i=1}^{k} w_i \hat{\theta}_i^2$$

with a χ_k^2 distribution.

Directional Test

A test of the more interesting directional alternative hypothesis that $\theta_i = \theta \neq 0$ for all i may be tested by comparing the quantity

$$X_D = \frac{\left(\sum_{i=1}^{k} w_i \hat{\theta}_i\right)^2}{\sum_{i=1}^{k} w_i}$$

with a χ_1^2 distribution. Note that this tests the hypothesis that all effects are equal to the same nonzero quantity.

Effect-Equality (Heterogeneity) Test

When the overall null hypothesis is rejected, the next step is to test whether all effects are equal, that is, whether the effects are homogeneous. Specifically, the hypothesis is

$$H_0 : \theta_i = \theta \quad i = 1, \cdots, k$$

versus the alternative that at least one effect is different, that is, that the effects are heterogeneous. This may also be interpreted as a test of the study-by-treatment interaction.

This hypothesis is tested using Cochran's Q test which is given by

$$Q = \sum_{i=1}^{k} w_i \left(\hat{\theta}_i - \hat{\theta}\right)^2$$

where

$$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

The test is conducted by comparing Q to a χ_{k-1}^2 distribution.

Fixed, Versus Random, Effects Combined Confidence Interval

If the effects are be assumed to be equal (homogeneous), either through testing or from other considerations, a *fixed effects model* may be used to construct a combined confidence interval. However, if the effects are heterogeneous, a *random effects model* should be used to construct the combined confidence interval.

Fixed Effects Model

The fixed effects model assumes homogeneity of study results. That is, it assumes that $\theta_i = \theta$ for all *i*. This assumption may not be realistic when combining studies with different patient pools, protocols, follow-up strategies, doses, durations, etc.

If the fixed effects model is adopted, the *inverse variance-weighted* method as described by Sutton (2000) page 58 is used to calculate the confidence interval for θ. The formulas used are

$$\hat{\theta} \pm z_{1-\alpha/2}\sqrt{\hat{V}(\hat{\theta})}$$

where $z_{1-\alpha/2}$ is the appropriate percentage point from the standardized normal distribution and

$$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

$$\hat{V}(\hat{\theta}) = \frac{1}{\sum_{i=1}^{k} w_i}$$

Random Effects Model

The random effects model assumes that the individual θ_i come from a random distribution with fixed mean $\bar{\theta}$ and variance σ^2. Sutton (2000) page 74 presents the formulas necessary to conduct a random effects analysis using the *weighted* method. The formulas used are

$$\hat{\bar{\theta}} \pm z_{1-\alpha/2}\sqrt{\hat{V}\left(\hat{\bar{\theta}}\right)}$$

where $z_{1-\alpha/2}$ is the appropriate percentage point from the standardized normal distribution and

$$\hat{\bar{\theta}} = \frac{\sum_{i=1}^{k} \bar{w}_i \hat{\theta}_i}{\sum_{i=1}^{k} \bar{w}_i}$$

$$\hat{V}\left(\hat{\bar{\theta}}\right) = \frac{1}{\sum_{i=1}^{k} \bar{w}_i}$$

$$\overline{w}_i = \frac{1}{\frac{1}{w_i} + \hat{\tau}^2}$$

$$\hat{\tau}^2 = \begin{cases} \dfrac{Q - k + 1}{U} & \text{if } Q > k - 1 \\[2mm] 0 & \text{otherwise} \end{cases}$$

$$Q = \sum_{i=1}^{k} w_i \left(\hat{\theta}_i - \hat{\theta}\right)^2$$

$$U = (k - 1)\left(\overline{w} - \frac{s_w^2}{k\overline{w}}\right)$$

$$s_w^2 = \frac{1}{k - 1}\left(\sum_{i=1}^{k} w_i^2 - k\overline{w}^2\right)$$

$$\overline{w} = \frac{1}{k}\left(\sum_{i=1}^{k} w_i\right)$$

Graphical Displays

A number of plots have been devised to display the information in a meta-analysis. These include the forest plot, the radial plot, and the L'Abbe plot. More will be said about each of these plots in the Output section.

Data Structure

The data are entered into a dataset using one row per study. The four counts of the study's 2-by-2 table are entered into four columns. In addition to these, an additional variable is usually used to hold a short (3 or 4 character) label. Another variable may be needed to hold a grouping variable.

As an example, we will use the METACPROP dataset which presents the results of 24 matched case-control studies that were conducted to study the effectiveness of a certain treatment. The goal of each study was to compare the proportion of cases that responding with a 'Yes' to the corresponding proportion of control responses with a 'Yes'. The studies were grouped into two diets, but these were not their main focus. These data are contained in the METACPROP database. You should load this database to see how the data are arranged.

Example 1 – Meta-Analysis of Correlated Proportions

This section presents an example of how to analyze the data contained in the MetaCProp dataset. This dataset contains data for 24 matched case-control studies. The response of each case subject was compared to the response of a matched control subject.

Setup

To run this example, complete the following steps:

1   Open the MetaCProp example dataset

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Select **MetaCProp** and click **OK**.

2   Specify the Meta-Analysis of Correlated Proportions procedure options

- Find and open the **Meta-Analysis of Correlated Proportions** procedure using the menus or the Procedure Navigator.
- The settings 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.

Variables Tab

N11 Count (A) Variable....................................**CaseYes**
N10 Count (B) Variable....................................**CaseNo**
N01 Count (C) Variable ....**ControlYes**
N00 Count (D) Variable ....**ControlNo**
Label Variable...**Study**
Group Variable..**Diet**
Combine Studies Using ....**Random Effects Method**
Change Zero Counts To (Delta).......................**0.0**

Reports Tab

Odds Ratio Reports/Plots ....**Checked**
Summary Report..**Checked**
Heterogeneity Tests..**Checked**
Outcome Detail Reports ....**Checked**

Plots Tab

Forest Plot ....**Checked**
Radial Plot ....**Checked**
L'Abbe Plot ....**Checked**

3   Run the procedure

- Click the **Run** button to perform the calculations and generate the output.

Run Summary Section

Run Summary Section

Parameter	Value	Parameter	Value
N11 Count (A) Variable	CaseYes	Rows Processed	24
N10 Count (B) Variable	CaseNo	Number Groups	2
N01 Count (C) Variable	ControlYes	Delta Value	0
N00 Count (D) Variable	ControlNo		
Row Label Variable	Study		
Group Variable	Diet		

Note: Check that the intended variables have been selected and number of rows is correct.

This report records the variables that were used and the number of rows that were processed.

Numeric Summary Section

Numeric Summary Section Using Random Effects Model

[Diet] Study	Data	P1	P2	Odds Ratio	Risk Ratio	Risk Difference
[A]						
S1	25/43 6/23	0.6515	0.4697	3.0000	1.3871	0.1818
S2	44/79 15/49	0.6172	0.4609	2.3333	1.3390	0.1563
S4	26/51 10/29	0.6375	0.4500	2.5000	1.4167	0.1875
S7	26/73 10/26	0.7374	0.3636	4.7000	2.0278	0.3737
S10	23/48 8/21	0.6957	0.4493	3.1250	1.5484	0.2464
S13	28/66 6/23	0.7416	0.3820	6.3333	1.9412	0.3596
S16	25/42 10/29	0.5915	0.4930	1.7000	1.2000	0.0986
S19	29/46 10/26	0.6389	0.5417	1.7000	1.1795	0.0972
S20	44/76 18/47	0.6179	0.5041	1.7778	1.2258	0.1138
S22	25/43 8/21	0.6719	0.5156	2.2500	1.3030	0.1563
S24	75/123 15/97	0.5591	0.4091	3.2000	1.3667	0.1500
Average				2.6640	1.4040	0.1906
[B]						
S3	53/72 21/43	0.6261	0.6435	0.9048	0.9730	-0.0174
S5	73/108 49/97	0.5268	0.5951	0.7143	0.8852	-0.0683
S6	58/97 37/103	0.4850	0.4750	1.0541	1.0211	0.0100
S8	42/74 18/47	0.6116	0.4959	1.7778	1.2333	0.1157
S9	56/98 14/39	0.7153	0.5109	3.0000	1.4000	0.2044
S11	71/112 21/63	0.6400	0.5257	1.9524	1.2174	0.1143
S12	60/108 28/89	0.5482	0.4467	1.7143	1.2273	0.1015
S14	46/81 15/49	0.6231	0.4692	2.3333	1.3279	0.1538
S15	58/77 21/43	0.6417	0.6583	0.9048	0.9747	-0.0167
S17	74/126 13/61	0.6738	0.4652	4.0000	1.4483	0.2086
S18	62/101 31/97	0.5101	0.4697	1.2581	1.0860	0.0404
S21	58/77 14/39	0.6638	0.6207	1.3571	1.0694	0.0431
S23	117/158 11/53	0.7488	0.6066	3.7273	1.2344	0.1422
Average				1.6166	1.1481	0.0804
[Combined]						
Average				1.9972	1.2448	0.1259

Note: This report shows the input data and the three outcomes for each study in the analysis. The 'Average' values are actually weighted averages with weights based on the effects model that was selected.

This report summarizes the input data. You should scan it for any mistakes. Note that the 'Average' lines provide the estimated group averages. The values depend on your selection of whether the Random Effects model or Fixed Effects model was used. The 'Combined' line provides the combined results of all studies.

Data

These are the count values that were read from the database.

P1

This is the estimated event proportion for variable 1 (the cases).

P2

This is the estimated event proportion for variable 2 (the controls).

Odds Ratio

This is the estimated value of the odds ratio. Note that it depends not only on the data, but also on the delta value used.

Risk Ratio

This is the estimated value of the risk ratio. Note that it depends not only on the data, but also on the delta value used.

Risk Difference

This is the estimated value of the risk difference. Note that it depends not only on the data, but also on the delta value used.

Nondirectional Zero-Effect Test

Nondirectional Zero-Effect Test

Diet	Outcome Measure	Chi-Square	DF	Prob Level
A	Odds Ratio	90.7010	11	0.0000
B	Odds Ratio	74.6044	13	0.0000
Combined	Odds Ratio	165.3054	24	0.0000

Note: This chi-square value tests the null hypothesis that all effects are zero versus the alternative that at least one study had a non-zero effect.

This reports the results of the nondirectional zero-effect chi-square test designed to test the null hypothesis that all treatment effects are zero. The null hypothesis is written

$$H_0 : \theta_i = 0 \quad i = 1, \cdots, k$$

The alternative hypothesis is that at least one $\theta_i \neq 0$, that is, at least one study had a statistically significant result.

Chi-Square

This is the computed chi-square value for this test. The formula was presented earlier.

DF

This is the degrees of freedom. For this test, the degrees of freedom is equal to the number of studies.

Prob Level

This is the significance level of the test. If this value is less than the nominal value of alpha (usually 0.05), the test is statistically significant, and the alternative is concluded. If the value is larger than the specified value of alpha, no conclusion can be drawn other than that you do not have enough evidence to reject the null hypothesis.

Directional Zero-Effect Test

Directional Zero-Effect Test

Diet	Outcome Measure	Chi-Square	DF	Prob Level
A	Odds Ratio	78.7597	1	0.0000
B	Odds Ratio	29.4196	1	0.0000
Combined	Odds Ratio	90.9788	1	0.0000

Note: This chi-square value tests the null hypothesis that all effects are zero versus the alternative that all studies had the same, non-zero effect.

This reports the results of the directional zero-effect chi-square test designed to test the overall null hypothesis that all treatment effects are zero. The null hypothesis is written

$$H_0 : \theta_i = 0 \quad i = 1, \cdots, k$$

The alternative hypothesis is that $\theta_i = \theta \neq 0$ for all i, that is, that all effects are equal to the same, non-zero value.

Chi-Square

This is the computed chi-square value for this test. The formula was presented earlier.

DF

This is the degrees of freedom. For this test, the degrees of freedom is equal to one.

Prob Level

This is the significance level of the test. If this value is less than the specified value of alpha (usually 0.05), the test is statistically significant, and the alternative is concluded. If the value is larger than the specified value of alpha, no conclusion can be drawn other than that you do not have enough evidence to reject the null hypothesis.

Effect-Equality (Heterogeneity) Test

Effect-Equality (Heterogeneity) Test

Diet	Outcome Measure	Cochran's Q	DF	Prob Level
A	Odds Ratio	11.9413	10	0.2890
B	Odds Ratio	45.1848	12	0.0000
Combined	Odds Ratio	74.3266	23	0.0000

Note: This tests the null hypothesis that all effects are equal (homogeneous) versus the alternative that at least one effect had a different effect (heterogeneous). Sometimes this test is used to choose between the use of a Fixed Effect (homogeneous) model and a Random Effects (heterogeneous) model.

This reports the results of the effect-equality (homogeneity) test. This chi-square test was designed to test the null hypothesis that all treatment effects are equal. The null hypothesis is written

$$H_0 : \theta_i = \theta \quad i = 1, \cdots, k$$

The alternative is that at least one effect is different, that is, that the effects are heterogeneous. This may also be interpreted as a test of the study-by-treatment interaction. This test may help you determine whether to use a Fixed Effects model (used for homogeneous effects) or a Random Effects model (heterogeneous effects).

Cochran's Q

This is the computed chi-square value for Cochran's Q statistic. The formula was presented earlier.

DF

This is the degrees of freedom. For this test, the degrees of freedom is equal to the number of studies minus one.

Prob Level

This is the significance level of the test. If this value is less than the specified value of alpha (usually 0.05), the test is statistically significant, and the alternative is concluded. If the value is larger than the specified value of alpha, no conclusion can be drawn other than that you do not have enough evidence to reject the null hypothesis.

Odds Ratio Detail Section

Odds Ratio Detail Section Using Random Effects Model

[Diet] Study	P1	P2	Odds Ratio	95.0% Lower Confidence Limit	95.0% Upper Confidence Limit	Percent Random Effects Weight
[A]						
S1	0.6515	0.4697	3.0000	1.1909	7.5576	3.0697
S2	0.6172	0.4609	2.3333	1.2744	4.2723	4.3247
S4	0.6375	0.4500	2.5000	1.2007	5.2051	3.7800
S7	0.7374	0.3636	4.7000	2.3750	9.3009	3.9902
S10	0.6957	0.4493	3.1250	1.4096	6.9280	3.5315
S13	0.7416	0.3820	6.3333	2.6773	14.9818	3.2895
S16	0.5915	0.4930	1.7000	0.7784	3.7126	3.5898
S19	0.6389	0.5417	1.7000	0.7784	3.7126	3.5898
S20	0.6179	0.5041	1.7778	0.9979	3.1671	4.4454
S22	0.6719	0.5156	2.2500	0.9783	5.1746	3.3928
S24	0.5591	0.4091	3.2000	1.7921	5.7140	4.4352
Average			2.6640	2.1011	3.3776	
[B]						
S3	0.6261	0.6435	0.9048	0.4864	1.6828	4.2560
S5	0.5268	0.5951	0.7143	0.4629	1.1022	5.0815
S6	0.4850	0.4750	1.0541	0.6722	1.6528	5.0115
S8	0.6116	0.4959	1.7778	0.9979	3.1671	4.4454
S9	0.7153	0.5109	3.0000	1.6385	5.4930	4.3247
S11	0.6400	0.5257	1.9524	1.1538	3.3035	4.6743
S12	0.5482	0.4467	1.7143	1.0756	2.7321	4.9400
S14	0.6231	0.4692	2.3333	1.2744	4.2723	4.3247
S15	0.6417	0.6583	0.9048	0.4864	1.6828	4.2560
S17	0.6738	0.4652	4.0000	2.1783	7.3452	4.3120
S18	0.5101	0.4697	1.2581	0.7850	2.0161	4.9156
S21	0.6638	0.6207	1.3571	0.6805	2.7067	3.9575
S23	0.7488	0.6066	3.7273	1.9158	7.2514	4.0623
Average			1.6166	1.2010	2.1759	
[Combined]						
Average			1.9972	1.5913	2.5065	

Note: This report presents the outcome's value as well as a confidence interval. The 'Average' line presents the combined estimates for the group. The weights let you determine the influence of each study on the combined results.

This report displays results for the odds ratio outcome measure. You can obtain a similar report for the risk ratio and the risk difference. The report gives you the
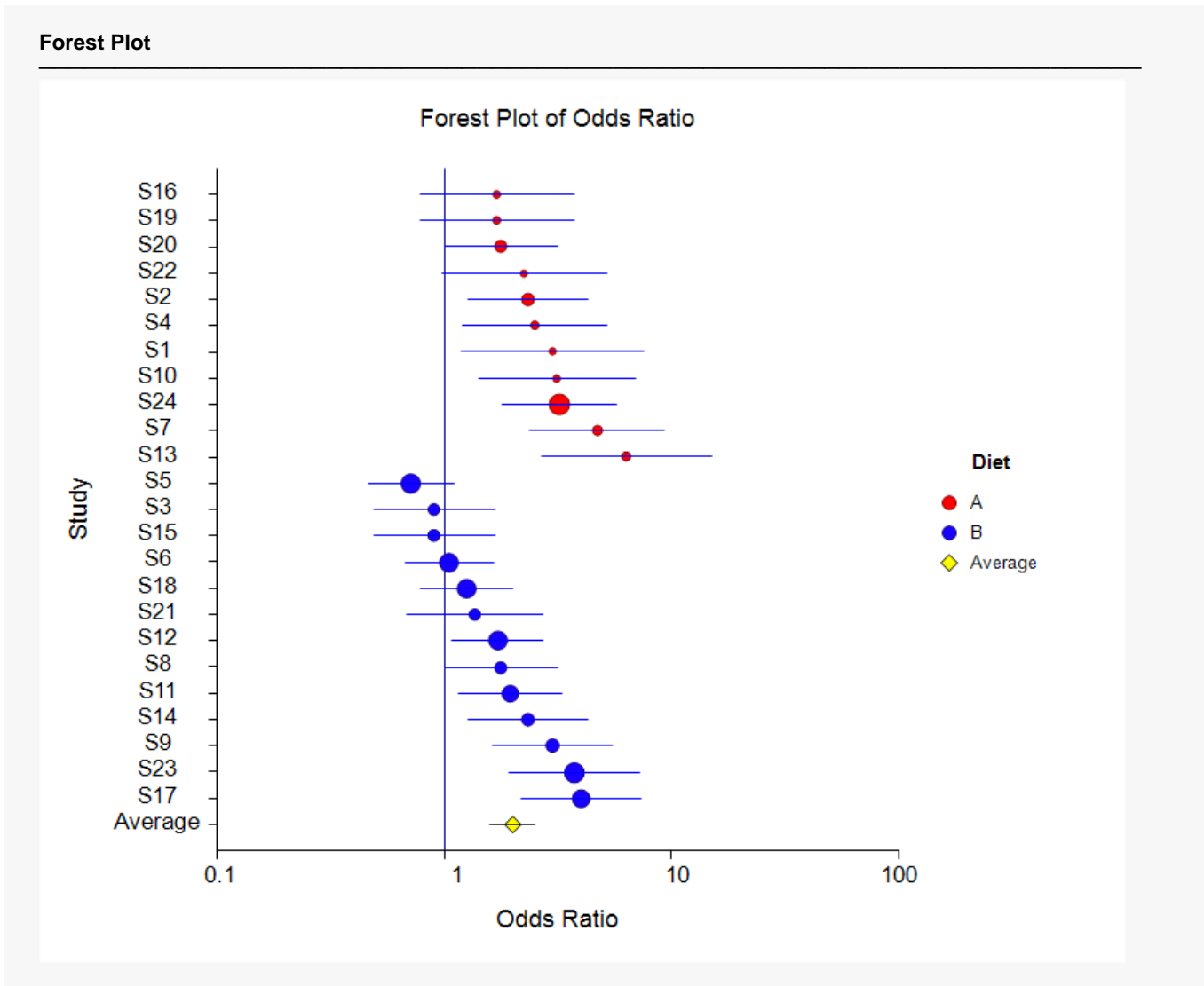
Confidence Limits

These are the lower and upper confidence limits (the formulas were given earlier in this chapter).

Weights

The last column gives the relative (percent) weight used in creating the weighted average. Using these values, you can decide how much influence each study has on the weighted average.

Forest Plot

Forest Plot
_____

This plot presents the results for each study on one plot. The size of the plot symbol is proportional to the sample size of the study. The points on the plot are sorted by group and by the odds ratio. The lines represent the confidence intervals about the odds ratios. Note that the narrower the confidence limits, the better.

By studying this plot, you can determine the main conclusions that can be drawn from the set of studies. For example, you can determine how many studies were significant (the confidence limits do not intersect the vertical line at 1.0). You can see if there were different conclusions for the different groups.

The results of the combining the studies are displayed at the end of each group.

Radial Plot

Radial Plot
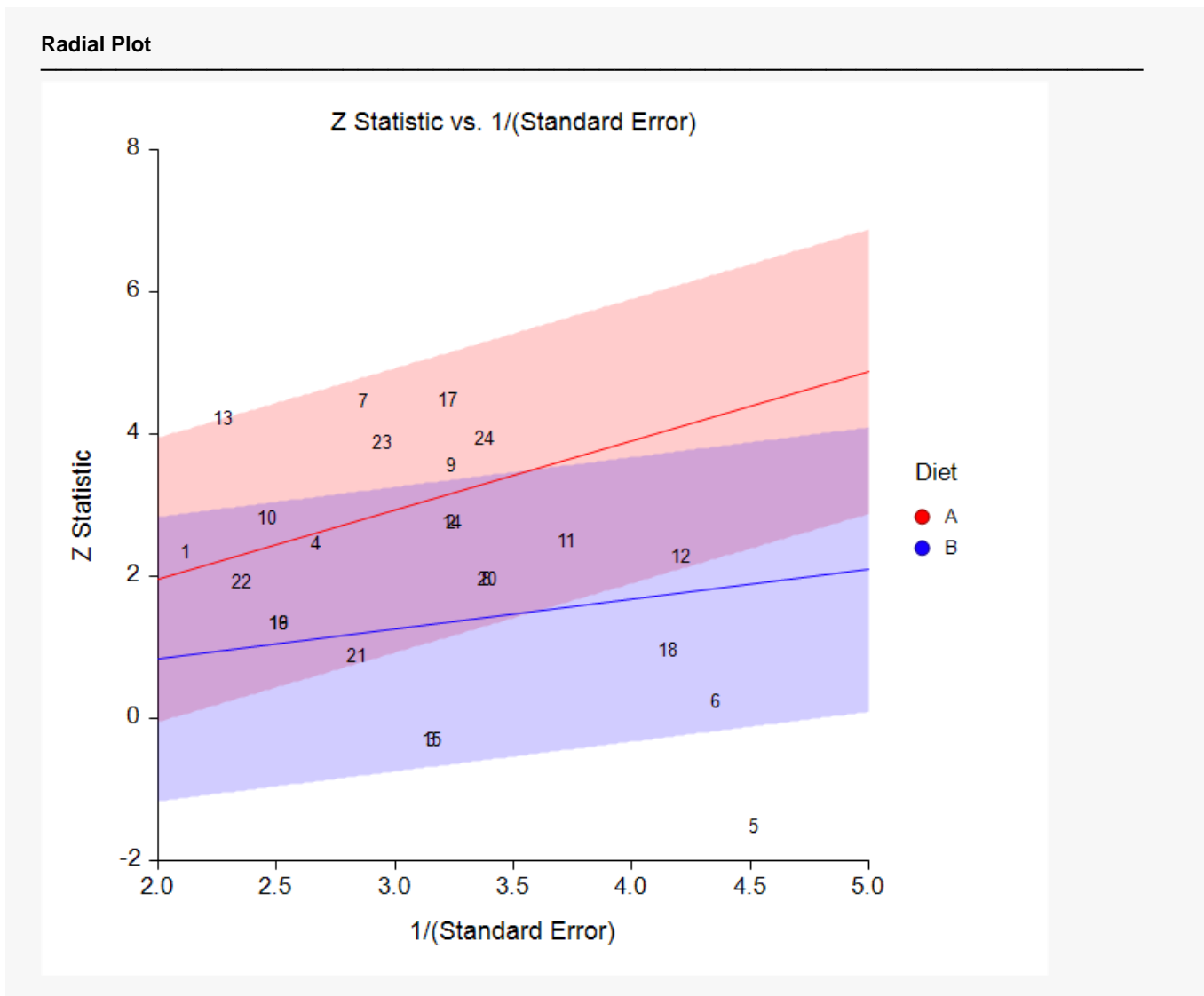
The radial (or Galbraith) plot shows the z-statistic (outcome divided by standard error) on the vertical axis and a measure of weight on the horizontal axis. Studies that have the largest weight are closest to the Y axis. Studies within the limits are interpreted as homogeneous. Studies outside the limits may be outliers.

L'Abbe Plot
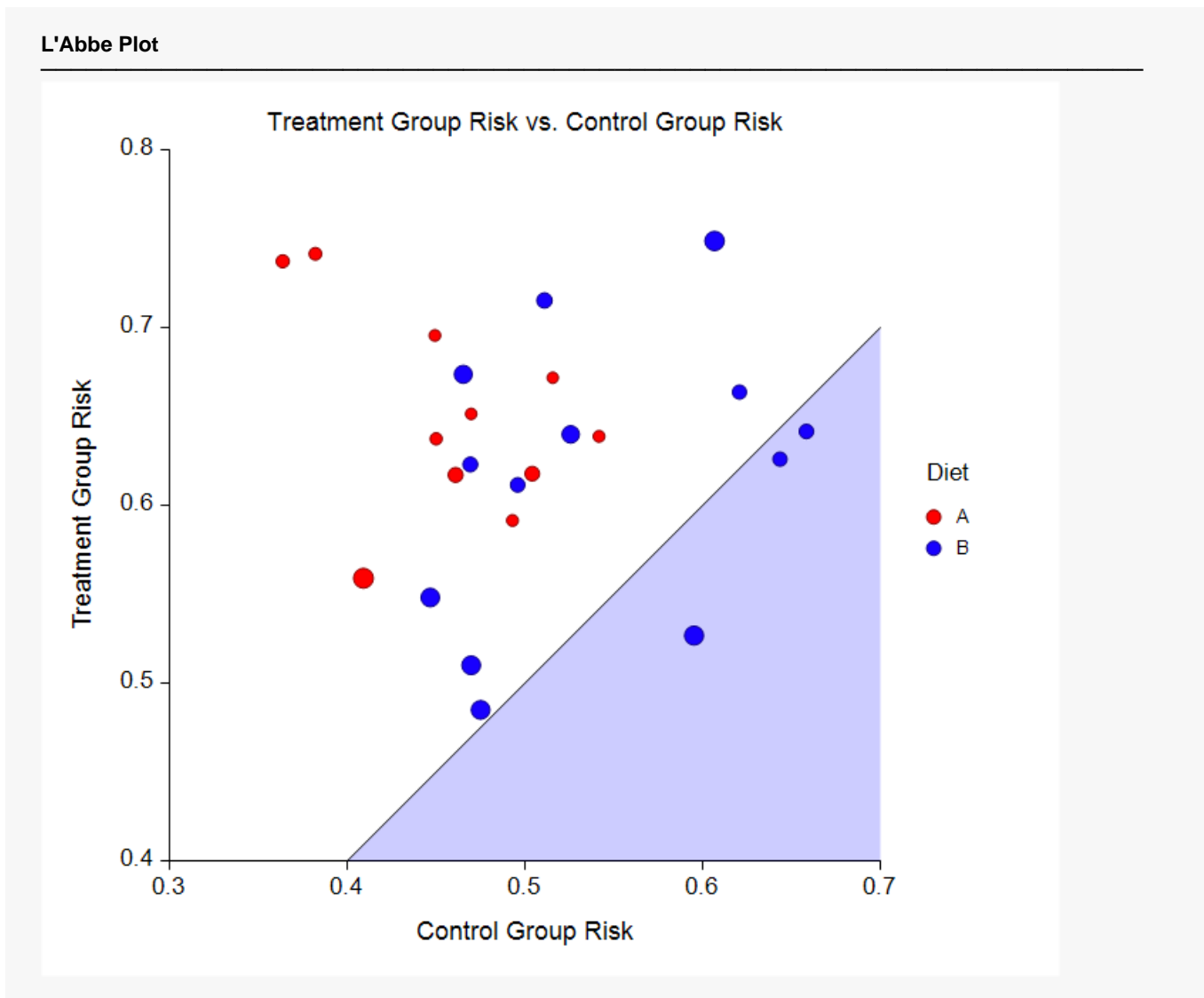
L'Abbe Plot
_____

The L'Abbe plot displays the variable 1 (case) proportion on vertical axis versus the variable 2 (control) proportion on the horizontal axis. Homogenous studies will be arranged along the diagonal line. This plot is especially useful in determining if the relationship between the two variables is the same for all values of variable 2.