

Chapter 456

Meta-Analysis of Proportions (Old Version)

Introduction

This module performs a meta-analysis of a set of two-group, binary-event studies. These studies have a treatment group (arm) and a control group. The results of each study may be summarized as counts in a 2-by-2 table. 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 $i = 1, \dots, k$. Each study consists of a treatment group (T) and a control group (C). The results of each study are summarized by four counts:

- a_i the number of subjects in the treatment group having the event of interest.
- b_i the number of subjects in the control group having the event of interest.
- c_i the number of subjects in the treatment group not having the event of interest.
- d_i the number of subjects in the control group not having the event of interest.

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.

Risks

These counts may be used to calculate estimates of the event-risk in the treatment group as

$$\hat{p}_{T_i} = \frac{a_i}{a_i + c_i}$$

and in the control group as

$$\hat{p}_{C_i} = \frac{b_i}{b_i + d_i}$$

Based on these risks, three measures of treatment effect may be defined and used in the meta-analysis. These are the odds ratio, the risk ratio, and the risk difference.

Odds Ratio

The odds ratio is the most commonly used measure of treatment effect. It is defined as follows.

$$OR_i = \frac{\frac{p_{T_i}}{1 - p_{T_i}}}{\frac{p_{C_i}}{1 - p_{C_i}}}$$

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. The variance of the sample log odds ratio is estimated by

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

Risk Ratio or Relative Risk

The risk ratio is calculated as follows.

$$RR_i = \frac{p_{T_i}}{p_{C_i}}$$

Like the odds ratio, the logarithm of the risk ratio is usually 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

$$\hat{V}(\ln(RR_i)) = \frac{1}{a_i} - \frac{1}{a_i + c_i} + \frac{1}{b_i} - \frac{1}{b_i + d_i}$$

Risk Difference

The risk difference is calculated as follows.

$$RD_i = p_{T_i} - p_{C_i}$$

The estimated variance of the sample risk difference is given by

$$\hat{V}(RD_i) = \frac{p_{T_i}(1 - p_{T_i})}{a_i + c_i} + \frac{p_{C_i}(1 - p_{C_i})}{b_i + d_i}$$

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

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

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

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

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

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

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

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

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^2_{k-1} distribution.

Fixed versus Random Effects Combined Confidence Interval

If the effects are 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

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

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

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

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

$$\bar{w}_i = \frac{1}{\frac{1}{w_i} + \hat{t}^2}$$

$$\hat{t}^2 = \begin{cases} \frac{Q - k + 1}{U} & \text{if } Q > k - 1 \\ 0 & \text{otherwise} \end{cases}$$

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

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

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

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

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 data referred to in Sutton (2000) as the cholesterol-lowering intervention dataset. This data set reviews 34 randomized clinical trials that were conducted to study the effects of three cholesterol-lowering treatments: diet, drug, and surgery. The mortality of patients in a treatment arm and a control arm were recorded. These data are contained in the SUTTON22 database. You should load this database to see how the data are arranged.

Example 1 – Meta-Analysis of Proportions

This section presents an example of how to analyze the data contained in the Sutton22 dataset. This dataset contains data for 34 randomized clinical trials that were conducted to study the effects of three cholesterol-lowering treatments: diet, drug, and surgery. The mortality of patients in a treatment arm and a control arm were recorded.

Setup

To run this example, complete the following steps:

1 Open the Sutton22 example dataset

- From the File menu of the NCSS Data window, select **Open Example Data**.
- Select **Sutton22** and click **OK**.

2 Specify the Meta-Analysis of Proportions procedure options

- Find and open the **Meta-Analysis of 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	
Treatment Event (A) Variable	TDeath
Control Event (B) Variable	CDeath
Treatment Nonevent (C) Variable	TSurvive
Control Nonevent (D) Variable.....	CSurvive
Label Variable.....	StudyID
Group Variable.....	Treatment
Reports Tab	
Show 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
Treatment Event-Count Variable	TDeath	Rows Processed	34
Treatment Nonevent-Count Variable	TSurvive	Number Groups	3
Control Event-Count Variable	CDeath	Delta Value	0.5
Control Nonevent-Count Variable	CSurvive		
Row Label Variable	StudyId		
Group Variable	Treatment		

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

[Treatment] StudyId	Data	P1	P2	Odds Ratio	Risk Ratio	Risk Difference
[Diet]						
S1	28/204 51/202	0.1373	0.2525	0.4750	0.5480	-0.1147
S7	41/206 55/206	0.1990	0.2670	0.6845	0.7477	-0.0676
S8	20/123 24/129	0.1626	0.1860	0.8529	0.8772	-0.0231
S9	111/1018 113/1015	0.1090	0.1113	0.9770	0.9795	-0.0023
S16	174/424 178/422	0.4104	0.4218	0.9542	0.9730	-0.0114
S17	28/199 31/194	0.1407	0.1598	0.8626	0.8821	-0.0190
S21	39/221 28/237	0.1765	0.1181	1.5910	1.4859	0.0582
S22	8/54 1/26	0.1481	0.0385	3.1075	2.7818	0.0990
S24	269/4541 248/4516	0.0592	0.0549	1.0835	1.0785	0.0043
Average				0.9292	0.9440	-0.0082
[Drug]						
S2	70/285 38/147	0.2456	0.2585	0.9305	0.9476	-0.0136
S3	37/156 40/119	0.2372	0.3361	0.6160	0.7077	-0.0986
S4	2/88 3/30	0.0227	0.1000	0.2271	0.2488	-0.0848
S5	0/30 3/33	0.0000	0.0909	0.1429	0.1567	-0.0868
S6	61/279 82/276	0.2186	0.2971	0.6636	0.7375	-0.0782
S10	81/427 27/143	0.1897	0.1888	0.9964	0.9971	-0.0006
S11	31/244 51/253	0.1270	0.2016	0.5801	0.6341	-0.0742
S12	17/50 12/50	0.3400	0.2400	1.6090	1.4000	0.0980
S13	23/47 20/48	0.4894	0.4167	1.3335	1.1702	0.0712
S15	1025/5552 723/2789	0.1846	0.2592	0.6470	0.7122	-0.0746
S18	42/350 48/367	0.1200	0.1308	0.9075	0.9187	-0.0107
S19	4/79 5/78	0.0506	0.0641	0.7965	0.8080	-0.0134
S20	37/1149 48/1129	0.0322	0.0425	0.7517	0.7597	-0.0103
S23	5/71 7/72	0.0704	0.0972	0.7223	0.7435	-0.0264
S26	0/94 1/94	0.0000	0.0106	0.3298	0.3333	-0.0105
S27	19/311 12/317	0.0611	0.0379	1.6293	1.5900	0.0232
S28	68/1906 71/1900	0.0357	0.0374	0.9534	0.9550	-0.0017
S29	44/2051 43/2030	0.0215	0.0212	1.0128	1.0125	0.0003
S30	33/6582 3/1663	0.0050	0.0018	2.4267	2.4194	0.0030
S31	236/5331 181/5296	0.0443	0.0342	1.3081	1.2945	0.0101

Meta-Analysis of Proportions (Old Version)

S32	0/48	1/49	0.0000	0.0204	0.3333	0.3401	-0.0198
S33	1/94	0/52	0.0106	0.0000	1.6845	1.6737	0.0064
S34	1/23	2/29	0.0435	0.0690	0.7333	0.7500	-0.0208
Average					0.8863	0.9108	-0.0115
[Surgery]							
S14	0/30	4/60	0.0000	0.0667	0.2058	0.2186	-0.0576
S25	46/421	62/417	0.1093	0.1487	0.7044	0.7369	-0.0393
Average					0.6885	0.7238	-0.0439
[Combined]							
Average					0.8868	0.9100	-0.0112

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 in the treatment group. This is also known as the treatment-group risk.

P2

This is the estimated event proportion in the control group. This is also known as the treatment-group risk.

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

Treatment	Outcome Measure	Chi-Square	DF	Prob Level
Diet	Odds Ratio	16.9314	9	0.0498
Drug	Odds Ratio	95.6162	23	0.0000
Surgery	Odds Ratio	3.9568	2	0.1383
Combined	Odds Ratio	116.5043	34	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

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

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

Treatment	Outcome Measure	Chi-Square	DF	Prob Level
Diet	Odds Ratio	0.1815	1	0.6701
Drug	Odds Ratio	33.7356	1	0.0000
Surgery	Odds Ratio	3.3032	1	0.0691
Combined	Odds Ratio	27.8056	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

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

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 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

Treatment	Outcome Measure	Cochran's Q	DF	Prob Level
Diet	Odds Ratio	16.7499	8	0.0328
Drug	Odds Ratio	61.8806	22	0.0000
Surgery	Odds Ratio	0.6536	1	0.4188
Combined	Odds Ratio	88.6987	33	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

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

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

[Treatment] StudyId	P1	P2	Odds Ratio	95.0% Lower Confidence Limit	95.0% Upper Confidence Limit	Percent Random Effects Weight
[Diet]						
S1	0.1373	0.2525	0.4750	0.2863	0.7882	3.5636
S7	0.1990	0.2670	0.6845	0.4327	1.0828	3.9108
S8	0.1626	0.1860	0.8529	0.4469	1.6277	2.7201
S9	0.1090	0.1113	0.9770	0.7405	1.2889	5.4463
S16	0.4104	0.4218	0.9542	0.7261	1.2538	5.4819
S17	0.1407	0.1598	0.8626	0.4976	1.4952	3.2731
S21	0.1765	0.1181	1.5910	0.9450	2.6788	3.4641
S22	0.1481	0.0385	3.1075	0.5128	18.8317	0.5279
S24	0.0592	0.0549	1.0835	0.9073	1.2940	6.2826
Average			0.9292	0.7641	1.1300	
[Drug]						
S2	0.2456	0.2585	0.9305	0.5902	1.4668	3.9372
S3	0.2372	0.3361	0.6160	0.3637	1.0434	3.4236
S4	0.0227	0.1000	0.2271	0.0424	1.2169	0.6012
S5	0.0000	0.0909	0.1429	0.0071	2.8849	0.1993
S6	0.2186	0.2971	0.6636	0.4526	0.9728	4.5216
S10	0.1897	0.1888	0.9964	0.6163	1.6111	3.7483
S11	0.1270	0.2016	0.5801	0.3578	0.9406	3.7285
S12	0.3400	0.2400	1.6090	0.6802	3.8059	1.8440
S13	0.4894	0.4167	1.3335	0.5983	2.9723	2.0452
S15	0.1846	0.2592	0.6470	0.5805	0.7211	6.7336
S18	0.1200	0.1308	0.9075	0.5842	1.4099	4.0500
S19	0.0506	0.0641	0.7965	0.2200	2.8836	0.9656
S20	0.0322	0.0425	0.7517	0.4868	1.1605	4.0985
S23	0.0704	0.0972	0.7223	0.2283	2.2857	1.1648
S26	0.0000	0.0106	0.3298	0.0133	8.1997	0.1750
S27	0.0611	0.0379	1.6293	0.7867	3.3743	2.3350
S28	0.0357	0.0374	0.9534	0.6802	1.3362	4.9093
S29	0.0215	0.0212	1.0128	0.6638	1.5452	4.1928
S30	0.0050	0.0018	2.4267	0.8059	7.3071	1.2530
S31	0.0443	0.0342	1.3081	1.0740	1.5934	6.1288
S32	0.0000	0.0204	0.3333	0.0132	8.3867	0.1737
S33	0.0106	0.0000	1.6845	0.0674	42.0926	0.1744
S34	0.0435	0.0690	0.7333	0.0898	5.9856	0.3966
Average			0.8863	0.7345	1.0696	
[Surgery]						
S14	0.0000	0.0667	0.2058	0.0107	3.9513	0.2060
S25	0.1093	0.1487	0.7044	0.4692	1.0575	4.3237
Average			0.6885	0.4603	1.0297	
[Combined]						
Average			0.8868	0.7739	1.0161	

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

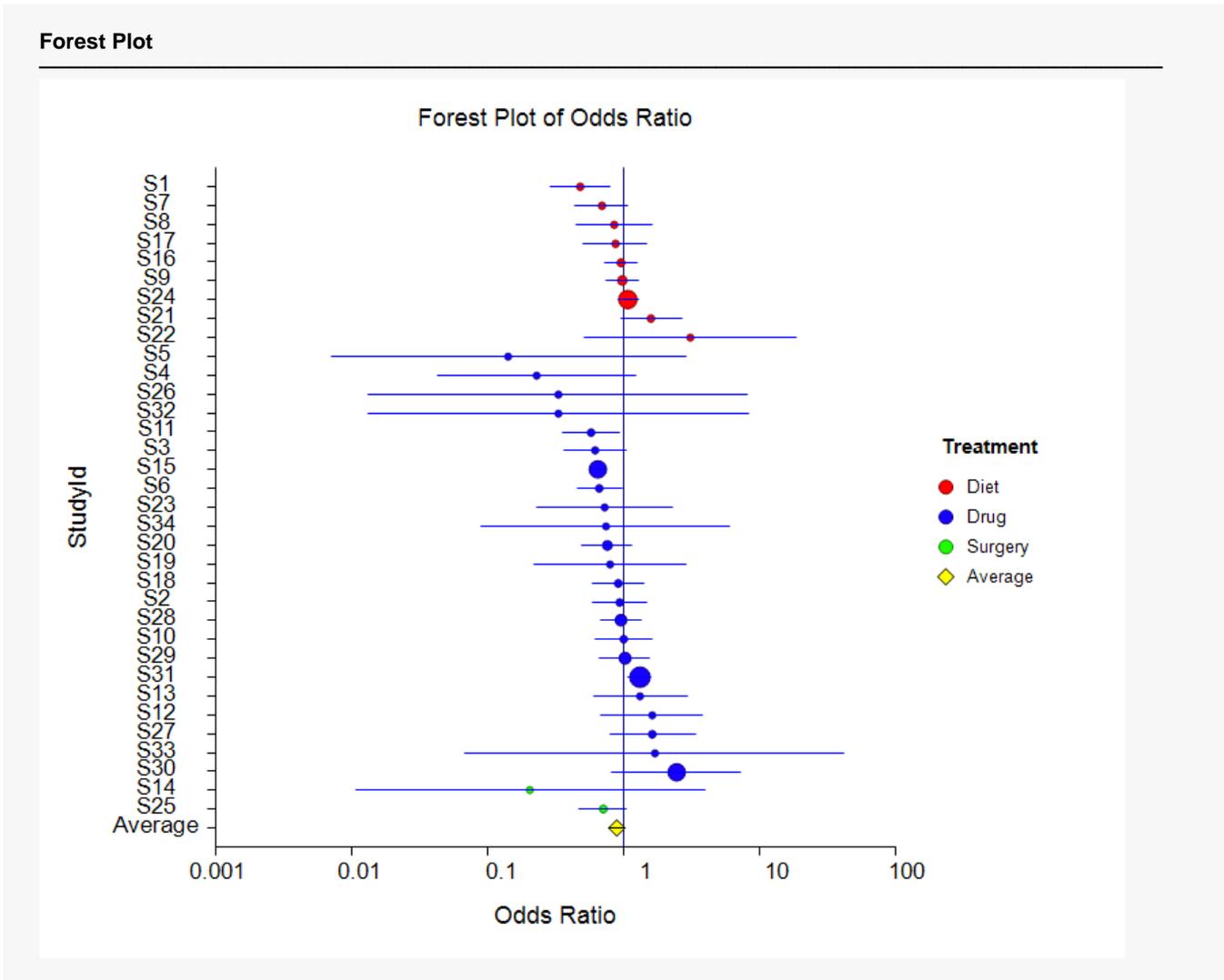
Confidence Limits

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

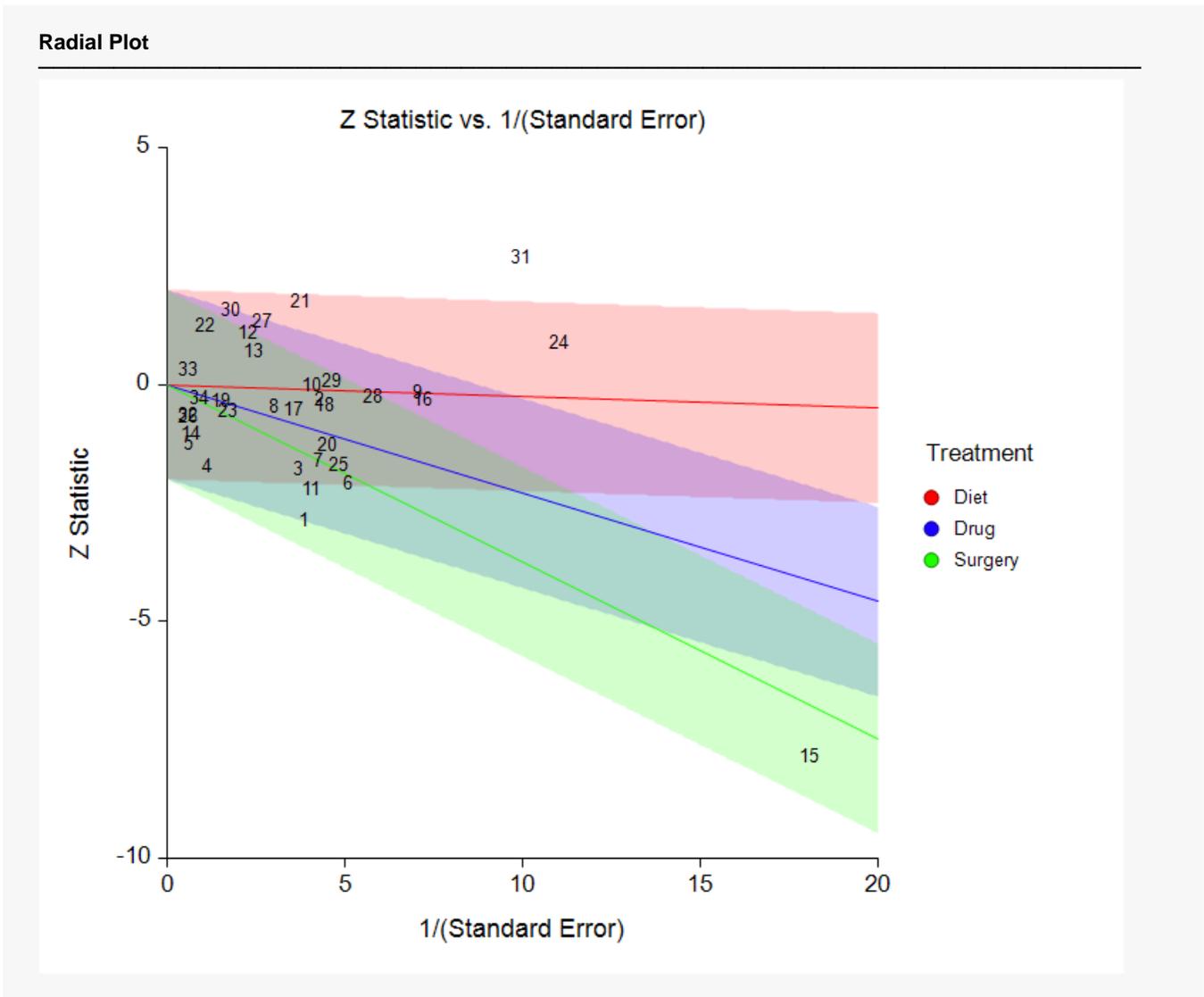


This plot presents the results for each study on one plot. The size of the plot symbol is proportional to the sample size of the study. The points on the plot are sorted by group and by the odds ratio. The lines represent the confidence intervals about the odds ratios. Note that the narrower the confidence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

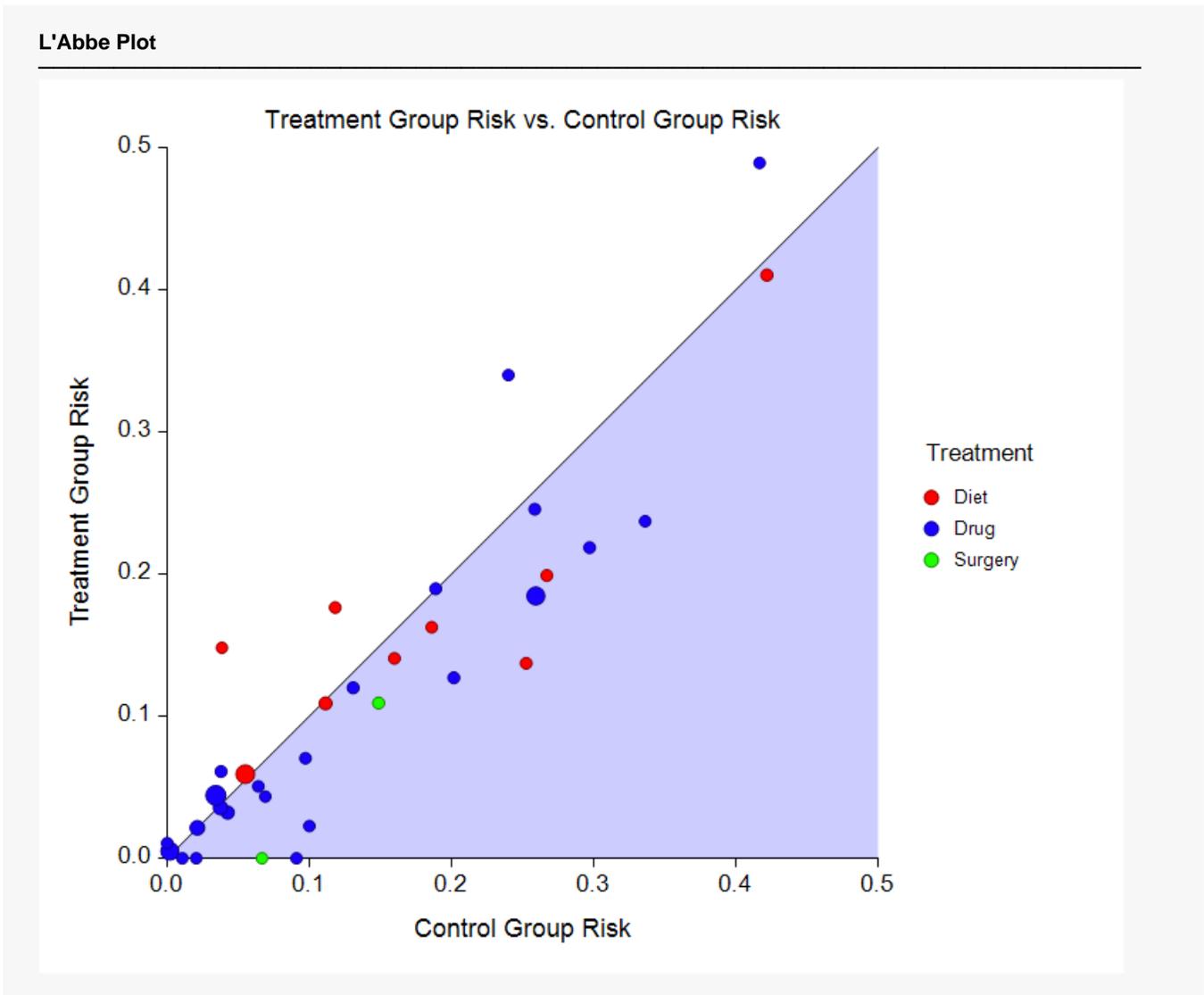
The results of the combining the studies are displayed at the end of each group.

Radial Plot



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



The L'Abbe plot displays the treatment risk on vertical axis versus the control risk 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 treatment group and the control group is the same for all values of the control group risk.