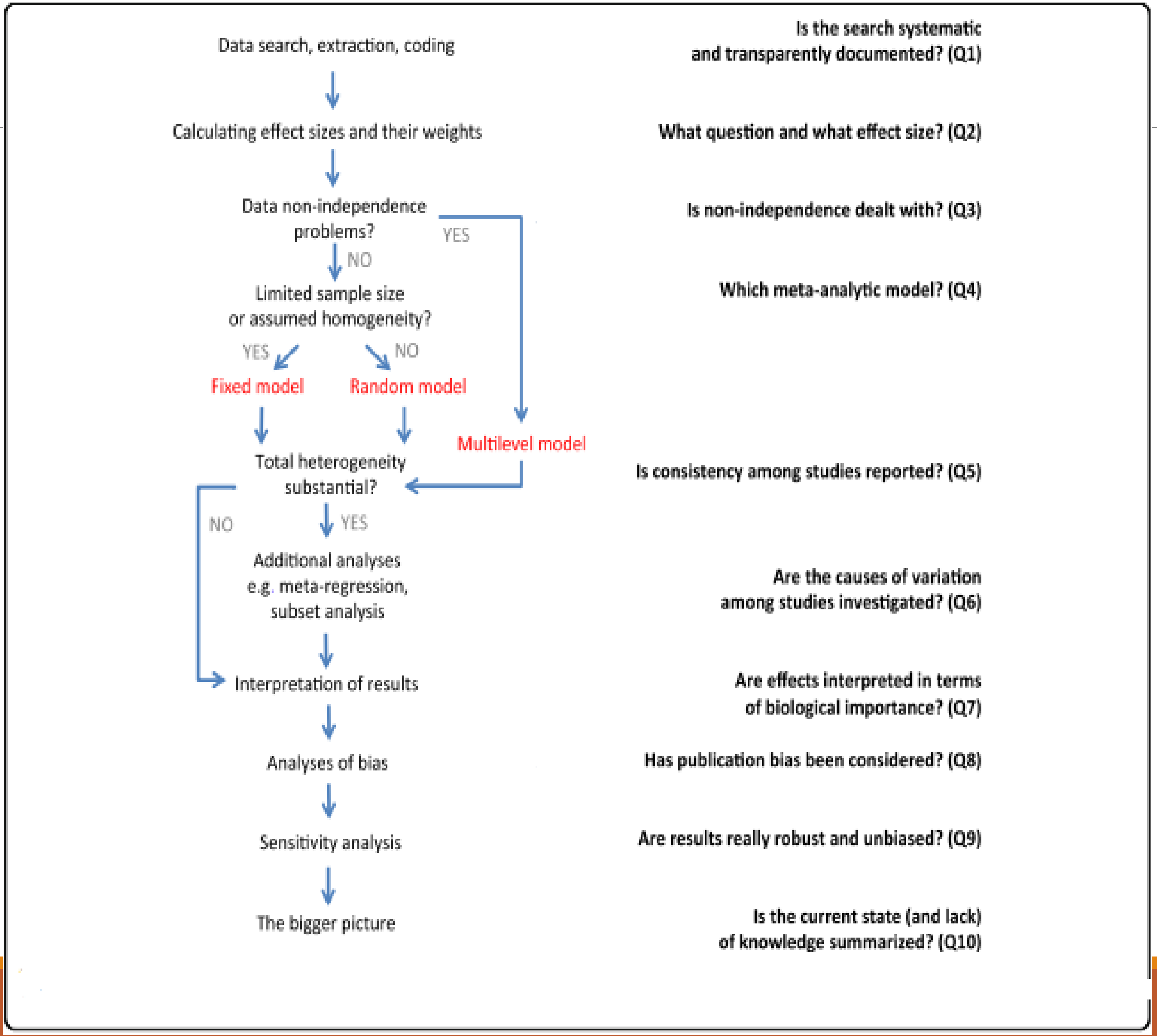
Stata 16 Meta Analysis

Steps of doing meta analysis



Description

Meta-analysis is a statistical technique for combining the results from several similar studies. The results of multiple studies that answer similar research questions are often available in the literature.

It is natural to want to compare their results and, if sensible, provide one unified conclusion. This is precisely the goal of the meta-analysis, which provides a single estimate of the effect of interest computed as the weighted average of the study-specific effect estimates.

When these estimates vary substantially between the studies, meta-analysis may be used to investigate various causes for this variation.

Another important focus of the meta-analysis may be the exploration and impact of small-study effects, which occur when the results of smaller studies differ systematically from the results of larger studies.

One of the common reasons for the presence of small-study effects is publication bias, which arises when the results of published studies differ systematically from all the relevant research results.

Main Components of Meta-Analysis

Effect sizes (or various measures of outcome) and their standard errors are the two most important components of a meta-analysis.

Forest plots, summarizes meta data in a graphical format. The results of meta-analysis are typically summarized on a forest plot, which plots the study-specific effect sizes and their corresponding confidence intervals, the combined estimate of the effect size and its confidence interval, and other summary measures such as heterogeneity statistics.

Heterogeneity, The estimates of effect sizes from individual studies will inherently vary from one study to another. This variation is known as a study heterogeneity.

Publication bias, The selection of studies in a meta-analysis is an important step. Ideally, all studies that meet prespecified selection criteria must be included in the analysis. This is rarely achievable in practice. For instance, it may not be possible to have access to some unpublished results. So some of the relevant studies may be omitted from the meta-analysis. This may lead to what is known in statistics as a sample-selection problem. In the context of meta-analysis, this problem is known as publication bias or, more generally, reporting bias.

Preparation Data, Declaration data

The declaration of your data to be meta data is the first step of your meta-analysis in Stata. Meta data are your original data that also store key variables and characteristics about your specifications, which will be used by all meta commands during your meta-analysis session.

Use meta set, If you have access only to precomputed effect sizes and their standard errors.

Use meta esize, If you have access to summary data such as means and standard deviations from individual studies, to compute the effect sizes and their standard errors and declare them.

Meta set

Two main components of meta-analysis are study-specific effect sizes and their precision. You must specify them during declaration.

with meta set, we must specify the variables containing **effect sizes** and their **standard errors**.

.meta set effectsize standardeviation

In descriptive studies is most useful.

Notice: Some analysis may not be available after meta set such as the Mantel–Haenszel estimation method and Harbord's test for the funnel-plot asymmetry because they require access to summary data.

Meta esize for Continous Data

meta esize computes and declares various effect sizes for two-group comparison of continuous outcomes

specify the number of observations, means, and standard deviations for each treatment group (group 1) and control group (group 2).

also specify the type of the effect size.

. meta esize n1 m1 sd1 n2 m2 sd2   Stata Command for Continous Data

Hedges's g standardized mean difference are the default, but you can specify others in the esize() option.

For the Hedges's g effect size, there are two ways to compute the bias-correction factor used in its formula.

For consistency with meta-analysis literature, meta esize uses an approximation, but you can specify the exact option within esize() to use the exact computation:

. meta esize n1 m1 sd1 n2 m2 sd2, esize(hedgesg, exact)

Meta esize for Continous Data

There is 4 others effect sizes in stata 17; Cohen's d, Glass's Delta1, Glass's Delta2, Mean difference

Both Hedges's g and Cohen's d effect sizes support standard error adjustment of Hedges and Olkin (1985) with esize()'s option holkinse:

. meta esize n1 m1 sd1 n2 m2 sd2, esize(cohend, holkinse)

For the (unstandardized) mean difference, you can choose to compute standard errors assuming

unequal variance between the two groups:

.meta esize n1 m1 sd1 n2 m2 sd2, esize(mdiff, unequal)

Meta esize for binary Data

With binary data, the effect measure can be difference between proportions (sometimes called the risk difference or absolute risk reduction), the ratio of two proportions (risk ratio or relative risk), or the odds ratio.

. meta esize n11 n12 n21 n22 Stata Command for Binary Data

Notice: If a study's 2 by 2 table contains one or more zero cells, then computational difficulties may be encountered in both the inverse variance and the Mantel–Haenszel methods. By default, it adds 0.5 to all cells of the 2 by 2 tables that contain at least one zero cell.

Meta Analysis Model

The role of a meta-analysis model is important for the computation and interpretation of the meta analysis results. Different meta-analysis models make different assumptions and, as a result, estimate different parameters of interest.

Common-effect:

A common-effect model makes a strong assumption about the underlying true effect size being the same across (common to) all studies.

Fixed-effects,

A fixed-effects model allows the effect sizes to be different across studies and assumes that they are fixed.

Random-effects

a random-effects model assumes that the study effect sizes are random, meaning that they represent a random sample from a larger population of similar studies. The results obtained from a random-effects model can be extended to the entire population of similar studies and not just the ones that were selected in the meta-analysis. The meta-analysis literature recommends to start with a random-effects model, which is also Stata's default for most meta commands.

which model should you choose?

Our recommendation is to start with a random-effects model and explore the heterogeneity, publication bias, and other aspects of your meta-analysis data.

If you are willing to assume that the studies have different true effect sizes and you are interested only in providing inferences about these specific studies, then the FE model is appropriate.

If the assumption of study homogeneity is reasonable for your data, a CE model may be considered

We suggest that you avoid using, or at least starting with, a common-effect model unless you verified that the underlying assumption of the common study effects is plausible for your data.

Random-effects model is Stata's default for most meta-analyses.

Notice: a fixed-effects model and a common-effect model produce the same results in a meta-analysis.

Fixed-Effects Model & Common-Effect Model

Although the final estimates are the same, their interpretation is different!

In a common-effect model, the estimate of the overall effect size is an estimate of the true common effect size,

In a fixed-effects model, it is an estimate of the average of true, different study-specific effect sizes.

When you assume a common-effect model, you essentially imply that certain issues such as study heterogeneity are of no concern in your data.

When you specify the common option, certain commands such as meta regression will not be available

Note: For other meta commands, specifying common versus fixed will merely change the reported title from, say, “Common-effect meta-analysis” to “Fixed-effects meta-analysis”.

Interpretation of Different Models

Table 1. Interpretation of θ_{pop} under various meta-analysis models.

CE and FE models are computationally identical but conceptually different.

Model	Interpretation of θ_{pop}
common-effect	common effect ($\theta_1 = \theta_2 = \ldots = \theta_K = \theta$)
fixed-effects	weighted average of the K true study effects
random-effects	mean of the distribution of $\theta j = \theta + u_j$

Random Effects Model

A random-effects (RE) meta-analysis model assumes that the study effect sizes are different and that the collected studies represent a random sample from a larger population of studies.

An RE meta-analysis model assumes that the study contributions, u_j ’s, are random.

It decomposes the variability of the effect sizes into the between-study and within-study components.

The within study variances, $\hat{\sigma}_j^2$ ’s, are assumed known by design.

The between-study variance, τ^2 , is estimated from the sample of the effect sizes.

Thus, the extra variability attributed to tau2 is accounted for during the estimation of the mean effect size, $E(\theta_j)$.

Command Meta Set

.meta set es se

The summary is divided into four categories:1- information about the study, 2- the specified effect sizes, 3- their precision, 4- meta-analysis model and method.

1- The study information consists of the number of studies (15 in our example), a study label (Generic), and a study size (N/A). If the studylabel (varname) option is specified, the Study label: will contain the name of the specified variable. Otherwise, a generic study label—Study 1, Study 2, and so on—will be used in the output of meta commands.

If the studysize (varname) option is specified with meta set, the Study size: will contain the name of the specified variable.

2- The effect-size information consists of the type of the effect size, its label, and the variable containing study-specific effect sizes. The effect-size Type: is always Generic with meta set. The effect-size Label: is either a generic Effect Size or as specified in the eslabel (string) option. This label will be used to label the effect sizes in the output of all meta commands. The effect-size Variable: displays the name of the declared variable containing effect sizes.

Command Meta Set

3- The precision information consists of variables containing effect-size standard errors, confidence intervals, and the declared confidence level. As with the effect sizes, meta set uses the standard errors specified in the sevar variable (variable se here). The corresponding confidence intervals are computed using the effect sizes and their standard errors and stored in the system variables meta cil and meta ciu. With meta set, you can specify confidence intervals instead of the standard errors.

4- the meta-analysis model and the meta-analysis estimation method are important aspects of your meta-analysis.

Data example for met set

var1	meanC	nC	SdC
Study 1	48.7	140	4.5
Study 2	51.2	164	6.3
Study 3	48.4	115	5.2
Study 4	49.6	205	4.1
Study 5	52.3	95	6.7
Study 6	49.6	321	2.5
Study 7	55.3	289	3.8
Study 8	49.4	190	4.1
Study 9	51.2	158	4.9
Study 10	55.6	257	5.6
Study 11	53.2	421	3.9
Syudy 12	50.4	367	5.5
Studt 13	51.6	127	4.9
Study 14	49.5	288	3.8
study 15	50.4	354	6.7

command

.gen sdmeanC= SdC/ nC^0.5

We can estimate the effect size standard deviation.

.meta set meanC sdmeanC

To declare data in meta format

Out Put after meta set

Meta-analysis setting information

Study information

No. of studies: 15

Study label: Generic

Study size: N/A

Effect size

Type: <generic>

Label: Effect size

Variable: meanC

Precision

Std. err.: sdmeanC

CI: [_meta_cil, _meta_ciu]

CI level: 95%

Model and method

Model: Random effects

Method: REML

Command meta esize for continuous data

meta esize nT meanT SdT nC meanC SdC

The meta setting information from meta esize is almost the same as the one produced by meta set.

1- The study information

As we mentioned earlier, meta esize computes the effect sizes and their standard errors from the specified summary data, so effect-size Variable: and Std. Err.: contain the names of the corresponding system variables, meta es and meta se. The summary data also include the information about the study size, so Study size: displays the name of the system variable, meta studysize, that contains study size, which is equal to the sum of n1 and n2 in our example.

Command meta esize continuous data

2- The effect-size information

meta esize computes the Hedges's g effect size for the two-group mean comparison.

You can specify the esize (esspec) option to select a different effect size. For the Hedges's g effect size, there are two methods to compute the underlying bias-correction term: approximate or exact.

For consistency with the meta-analysis literature, meta esize, by default, uses an approximation, as indicated in Bias correction: under Effect size.

But you can change this by specifying the exact option within esize().

Command meta esize continuous data

3- The precision information

This adjustment is applicable only with the Hedges's g or Cohen's d effect size. No adjustment is made by default, but you can use the holkinse option within esize() to specify the adjustment of Hedges and Olkin (1985).

For the mean-difference effect size, you can request the adjustment for unequal group variances by specifying esize()'s option unequal.

4- Model and Method

For log odds-ratios or log risk-ratios, meta esize additionally reports the type of adjustment made to the zero cells of contingency tables, which represent the summary data for binary outcomes.

For these effect sizes, the type of adjustment will be listed in Zero-cells adj.: under Effect size (not applicable in our example). By default, 0.5 is added to each zero cell, but you can specify the zerocells() option with meta esize to apply a different adjustment or none.

Data example for met esize

var1	meanC	nC	SdC	meanT	SdT	nT
Study 1	48.7	140	4.5	49.2	3.8	150
Study 2	51.2	164	6.3	53.1	4.5	156
Study 3	48.4	115	5.2	47.9	5.6	105
Study 4	49.6	205	4.1	51.4	6.3	200
Study 5	52.3	95	6.7	50.2	4.8	110
Study 6	49.6	321	2.5	51.2	5.2	350
Study 7	55.3	289	3.8	56.3	4.1	320
Study 8	49.4	190	4.1	53.5	3.8	201
Study 9	51.2	158	4.9	52.4	4.6	165
Study 10	55.6	257	5.6	57.4	4.1	315
Study 11	53.2	421	3.9	51.3	3.9	450
Syudy 12	50.4	367	5.5	55.2	6.5	368
Studt 13	51.6	127	4.9	48.3	6.5	145
Study 14	49.5	288	3.8	50.3	4.6	296
study 15	50.4	354	6.7	52.5	3.5	405

Stata Output after meta esize command

Study information

No. of studies: 15
Study label: Generic
Study size: _meta_studysize
Summary data: nC meanC SdC nT meanT SdT

Effect size

Type: cohend
Label: Cohen's d
Variable: _meta_es

Precision

Std. err.: _meta_se
Std. err. adj.: None
CI: [_meta_cil, _meta_ciu]
CI level: 95%

Model and method

Model: Random effects
Method: REML

System variables

meta system variables are the variables that begin with meta . There are four main variables

that are stored by the two commands.

1- _meta es: stores study-specific effect sizes.

2- _meta se: stores the standard errors of study-specific effect sizes..

3- _meta cil and _meta ciu store the lower and upper limits of the CIs for study-specific effect sizes.

These variables correspond to the confidence level declared for the meta-analysis, the value of which is stored in the data characteristic meta level.

4- integer study identifiers stored in _meta id, study labels stored in a string variable meta studylabel, and study sizes stored in _meta studysize.

_meta studysize is always stored with meta esize.

With meta set, it is stored only when the variable containing study sizes is specified in the studysize() option.

Most popular Command in stata

.describe _meta*

With this command you can see the System variables name and characteristics, which created by meta set that will be used by other meta commands in the computations.

.meta summarize

It reports individual effect sizes and the overall effect size (ES), their confidence intervals (CIs), heterogeneity statistics, and more. meta summarize can perform random-effects (RE), common-effect (CE), and fixed-effects (FE) meta-analyses. It can also perform subgroup, cumulative, and sensitivity meta-analyses.

.meta query **or** **. meta query, short**

You can use meta query to describe the current meta-analysis settings with meta data in memory.

meta query produces the same output as meta set and meta esize. If the data in memory are not

Data Example

. use https://www.stata-press.com/data/r16/pupiliqset, clear

Recall the pupil IQ data (Raudenbush and Bryk 1985; Raudenbush 1984) described in Effects of teacher expectancy on pupil IQ (pupiliq.dta) of [META] meta.

Notice: This data has been definition in meta format.

. meta summarize

meta summarize out put

```
  Effect-size label:  Std. Mean Diff.
        Effect size:  stdmdiff
          Std. Err.:  se
        Study label:  studylbl

Meta-analysis summary                               Number of studies =     10
Random-effects model                                Heterogeneity:
Method: REML                                                    tau2 =  0.0754
                                                              I2 (%) =   74.98
                                                                  H2 =    4.00
```

Amount greater than 50% indicates considerable heterogeneity.

Effect Size: Std. Mean Diff.

Study	Effect Size	[95% Conf.	Interval]	% Weight
Rosenthal et al., 1974	0.030	-0.215	0.275	12.39
Conn et al., 1968	0.120	-0.168	0.408	11.62
Jose & Cody, 1971	-0.140	-0.467	0.187	10.92
Pellegrini & Hicks, 1972	1.180	0.449	1.911	5.25
Pellegrini & Hicks, 1972	0.260	-0.463	0.983	5.33
Evans & Rosenthal, 1969	-0.060	-0.262	0.142	13.11
Fielder et al., 1971	-0.020	[illegible]	[illegible]	[illegible]
Claiborn, 1969	[illegible]	[illegible]	[illegible]	[illegible]
Kester, 1969	[illegible]	[illegible]	[illegible]	[illegible]
Maxwell, 1970	0.800	[illegible]	1.292	8.15
theta	0.134	-0.075	0.342	

```
Test of theta = 0: z = 1.26                           Prob > |z| = 0.2085
Test of homogeneity: Q = chi2(9) = 26.21              Prob > Q = 0.0019
```

P-value less than 0.1 shown heterogeneity.

Forest Plot

.meta forestplot

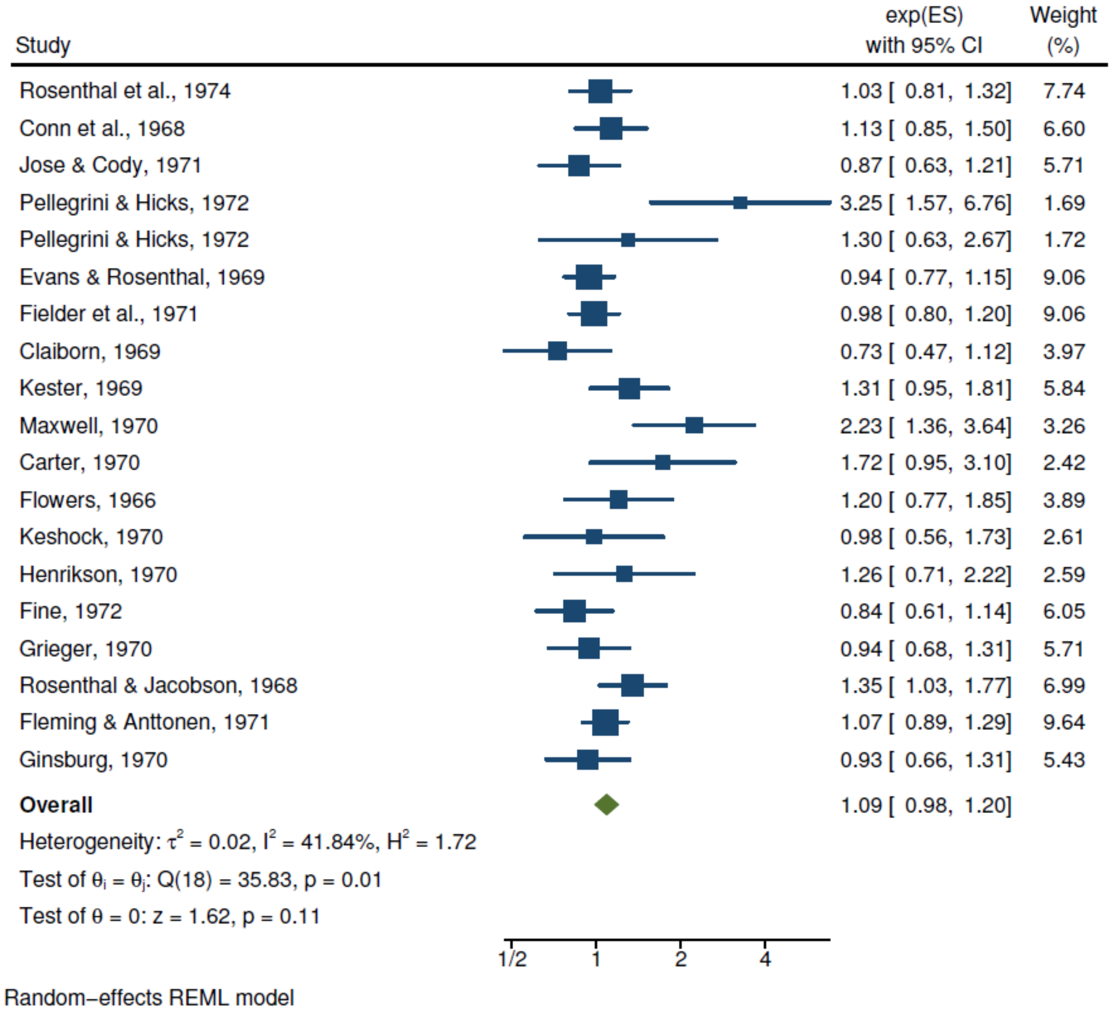
A forest plot shows study-specific effect sizes and an overall effect size with their respective confidence intervals.

The information about study heterogeneity and the significance of the overall effect size are also typically presented.

A blue square is plotted for each study, with the size of the square being proportional to the study weight; that is, larger squares correspond to larger (more precise) studies.

Studies' CIs are plotted as whiskers extending from each side of the square and spanning the width of the CI.

Forest Plot out put



Forest Plot

. meta forestplot

The estimate of the overall effect size, depicted here by a green diamond, is typically plotted following the individual effect sizes.

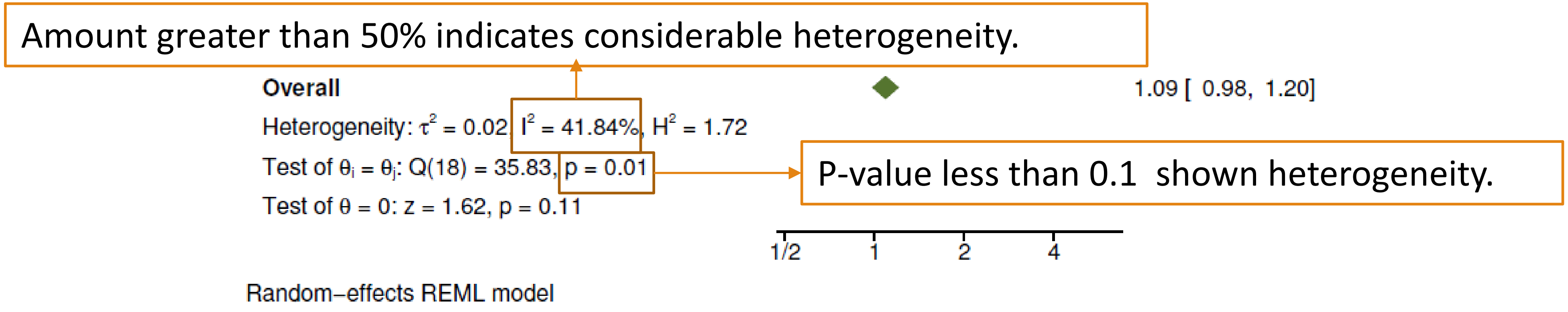
The diamond is centered at the estimate of the overall effect size and the width of the diamond represents the corresponding CI width.

Heterogeneity measures such as the I^2 and H^2 statistics, homogeneity test, and the significance test of the overall effect sizes are also commonly reported.

Assessing heterogeneity

Forest plots are useful for visual examination of heterogeneity. Its presence can be evaluated by looking at the plotted CIs, which are represented as horizontal lines on the plot. Heterogeneity is suspect if there is a lack of overlap between the CIs.

You can also test for heterogeneity more formally by using Cochrane's homogeneity test. Additionally, various heterogeneity measures such as the I^2 statistic, which estimates the percentage of the between-study variability, are available to quantify heterogeneity.



several strategies to address heterogeneity

1. Explore heterogeneity”. Subgroup analyses and meta-regression are commonly used to explore heterogeneity.

2. Perform an RE meta-analysis”. After careful consideration of subgroup analysis and metaregression, you may consider an RE meta-analysis to account for the remaining unexplained between-study heterogeneity.

3. “Exclude studies”. Generally, you should avoid excluding studies from a meta-analysis because this may lead to bias.

4. perform sensitivity analysis and report both the results with and without the outlying studies.

5. “Do not perform a meta-analysis”.

In the presence of substantial variation that cannot be explained, you may have to abandon the meta-analysis altogether.

In this case, it will be misleading to report a single overall estimate of an effect, especially if there is a disagreement among the studies about the direction of the effect.

Subgroup meta analysis

In the presence of substantial between-study variability, meta analysis may be used to explore the relationship between the effect sizes and study-level covariates of interest, known in the meta-analysis literature as moderators.

Subgroup meta-analysis is commonly used with categorical covariates

In subgroup meta-analysis ,the studies are grouped based on study or participants' characteristics, and an overall effect-size estimate is computed for each group.

The goal of subgroup analysis is to compare these overall estimates across groups and determine whether the considered grouping helps explain some of the observed between-study heterogeneity.

Meta regression

Meta-regression is used when at least one of the covariates is continuous.

Meta-regression explores a relationship between the study-specific effect sizes and the study-level covariates, such as a latitude of a study location or a dosage of a drug. These covariates are often referred to as moderators.

Two types of meta-regression are commonly considered in the meta-analysis literature: fixed-effects meta-regression and random-effects meta-regression.

Notice: It is recommended that you have at least 10 studies per moderator to perform meta-regression.

FE meta-regression

An FE meta-regression (Greenland 1987) assumes that all heterogeneity between the study outcomes can be accounted for by the specified moderators.

Let x_j be a p × 1 vector of moderators with the corresponding unknown coefficient vector, . An FE meta-regression is given by

$$\hat{\theta}_j = x_j\beta + \epsilon_j \qquad \text{weighted by } w_j = \frac{1}{\hat{\sigma}_j^2}, \text{ where } \epsilon_j \sim N(0, \hat{\sigma}_j^2)$$

A traditional FE meta-regression does not model residual heterogeneity, but it can be incorporated by multiplying each of the variances $\hat{\sigma}_j^2$, by a common factor.

This model is known as an FE meta-regression with a multiplicative dispersion parameter or a multiplicative FE meta-regression.

RE meta-regression

An RE meta-regression can be viewed as a meta-regression that incorporates the residual heterogeneity via an additive error term, which is represented in a model by a study-specific random effect.

These random effects are assumed to be normal with mean zero and variance τ^2, which estimates the remaining between-study heterogeneity that is unexplained by the considered moderators.

$$\widehat{\theta}_j = \mathbf{x}_j\beta + u_j + \epsilon_j \qquad \text{weighted by } w_j^* = \frac{1}{\widehat{\sigma}_j^2 + \widehat{\tau}^2}, \text{ where } u_j \sim N(0, \tau^2) \text{ and } \epsilon_j \sim N(0, \widehat{\sigma}_j^2)$$

Example

.use https://www.stata-press.com/data/r17/bcgset

.meta summarize

```
Random-effects model                        Heterogeneity:
Method: REML                                            tau2 =  0.3132
                                                      I2 (%) =   92.22
                                                          H2 =   12.86

--------------------------------------------------------------------------
                        Study | Log risk-ratio   [95% conf. interval]  % weight
--------------------------------------------------------------------------
              Aronson, 1948 |         -0.889     -2.008      0.229       5.06
      Ferguson & Simes, 1949 |         -1.585     -2.450     -0.721       6.36
      Rosenthal et al., 1960 |         -1.348     -2.611     -0.085       4.44
     Hart & Sutherland, 1977 |         -1.442     -1.719     -1.164       9.70
  Frimodt-Moller et al., 1973 |         -0.218     -0.661      0.226       8.87
       Stein & Aronson, 1953 |         -0.786     -0.949     -0.623      10.10
     Vandiviere et al., 1973 |         -1.621     -2.546     -0.695       6.03
           TPT Madras, 1980 |          0.012     -0.111      0.135      10.19
      Coetzee & Berjak, 1968 |         -0.469     -0.935     -0.004       8.74
      Rosenthal et al., 1961 |         -1.371     -1.901     -0.842       8.37
       Comstock et al., 1974 |         -0.339     -0.558     -0.121       9.93
     Comstock & Webster, 1969 |          0.446     -0.984      1.876       3.82
       Comstock et al., 1976 |         -0.017     -0.541      0.506       8.40
--------------------------------------------------------------------------
                        theta |         -0.715     -1.067     -0.362
--------------------------------------------------------------------------
Test of theta = 0: z = -3.97                        Prob > |z| = 0.0001
Test of homogeneity: Q = chi2(12) = 152.23            Prob > Q = 0.0000
```

Meta regression example

. meta regress latitude_c

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                    Number of obs  =         13
Method: REML                                      Residual heterogeneity:
                                                              tau2 =   .07635
                                                            I2 (%) =    68.39
                                                                H2 =     3.16
                                                     R-squared (%) =    75.63
                                                  Wald chi2(1)   =      16.36
                                                  Prob > chi2    =     0.0001
```

_meta_es	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
latitude_c	-.0291017	.0071953	-4.04	0.000	-.0432043	-.0149991
_cons	-.7223204	.1076535	-6.71	0.000	-.9333174	-.5113234

Test of residual homogeneity: Q_res = chi2(11) = 30.73   Prob > Q_res = 0.0012

Meta reg interpretation

The header includes the information about the meta-analysis model and reports various summaries such as heterogeneity statistics and the model test.

For example, the results are based on 13 studies.

In the meta summarize, can seen there is (I2) 92.22 percent heterogeneity, But after including latitude_c as the moderator this amounts reduce 68% of the variability in the residuals is still attributed to the between-study variation.

The adjusted R2 statistic can be used to assess the proportion of between-study variance explained by the covariates;

Here roughly 76% of the between-study variance is explained by the covariate latitude_c.

Meta reg interpretation

The output header also displays a model test that all coefficients other than the intercept are equal to zero based on the chi2 distribution with p-1 degrees of freedom. In our example, the chi2 test statistic is 16.36 with a p-value of 0.0001.

The regression coefficient for latitude-c is -0.029, which means that every one degree of latitude

corresponds to a decrease of 0.029 units in log risk-ratio. The intercept, b0, is -0.722, which means

that the overall risk ratio at the mean latitude (latitude-c = 0 corresponds to latitude=33.46) is exp(-0.722) = 0.46. Both of these coefficients are statistically significantly different from zero based on the reported z tests.

Finally, a test of residual homogeneity is reported at the bottom of the output. The test statistic Qres is 30.73 with a p-value of 0.0012, which suggests the presence of heterogeneity among the residuals.

More option in met regression

use of a different RE method, for instance, the Sidik–Jonkman method, instead of the default REML method.

. meta regress latitude_c, random(sjonkman)

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                    Number of obs   =         13
Method: Sidik-Jonkman                             Residual heterogeneity:
                                                              tau2 =   .2318
                                                            I2 (%) =   86.79
                                                                H2 =    7.57
                                                     R-squared (%) =   32.90
                                                  Wald chi2(1)    =     6.50
                                                  Prob > chi2     =   0.0108

------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
  latitude_c |  -.0280714   .0110142    -2.55   0.011    -.0496589   -.0064838
       _cons |  -.7410395   .1602117    -4.63   0.000    -1.055049   -.4270304
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(11) = 30.73   Prob > Q_res = 0.0012
```

Interpretation of Out Put

The estimate of the regression coefficient for latitude c is -0.028 and is similar to the REML estimate of -0.029, but the standard errors are quite different: 0.011 versus 0.007. Recall that REML assumes that the error distribution is normal, whereas the Sidik–Jonkman estimator does not.

The estimates of the between-study variance, tau2, are also very different: 0.23 compared with the REML estimate of 0.08.

More option in meta regression

use an alternative standard-error computation sometimes used in practice—the truncated Knapp–Hartung method.

meta regress latitude_c, se(khartung, truncated)

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                    Number of obs   =         13
Method: REML                                      Residual heterogeneity:
SE adjustment: Truncated Knapp–Hartung                       tau2 =   .07635
                                                           I2 (%) =    68.39
                                                               H2 =     3.16
                                                    R-squared (%) =    75.63
                                                  Model F(1,11)   =    12.59
                                                  Prob > F        =   0.0046
------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      t    P>|t|     [95% conf. interval]
-------------+----------------------------------------------------------------
  latitude_c |  -.0291017   .0082014    -3.55   0.005    -.0471529   -.0110505
       _cons |  -.7223204   .1227061    -5.89   0.000    -.9923946   -.4522462
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(11) = 30.73   Prob > Q_res = 0.0012
```

Interpretation of Out Put

The reported standard errors are larger than, this is expected because the Knapp–Hartung adjustment incorporates the uncertainty in estimating tau2 in the standard error computation.

Also, the inferences for the tests of coefficients and the model test are now based on the Student’s t and F distributions, respectively, instead of the default normal and chi2 distributions.

Fixed meta regression

The use of an FE meta-regression is usually discouraged in the meta-analysis literature because it assumes that all between-study heterogeneity is accounted for by the specified moderators. This is often an unrealistic assumption in meta-analysis.

meta regress latitude_c, fixed

Because the FE regression assumes no additional residual heterogeneity, the residual heterogeneity statistics and the residual homogeneity test are not reported with meta regress, fixed.

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Fixed-effects meta-regression                    Number of obs   =        13
Method: Inverse-variance                         Wald chi2(1)    =    121.50
                                                 Prob > chi2     =    0.0000
```

_meta_es	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
latitude_c	-.0292369	.0026524	-11.02	0.000	-.0344356	-.0240383
_cons	-.6347482	.0445446	-14.25	0.000	-.7220541	-.5474423

Interpretation of Out Put

The coefficient estimates are similar to random effect, but standard errors from the FE regression are smaller. This is because the FE regression does not account for the residual heterogeneity that is not explained by the included moderators.

Constatn met regression

To fit a constant-only model with many regression estimation commands use

.meta regress _cons

Note that the estimated value of tau2 is now 0.313, whereas in random effect it was 0.076.

That is, the inclusion of covariate latitude_c reduced tau2 from 0.313 to 0.076 for a relative reduction of (0.313-.076)/0.313 =76%.

Notice: constant meta-regression produces the same results as a standard meta-analysis.

```
Effect-size label: Log risk-ratio
      Effect size: _meta_es
        Std. err.: _meta_se

Random-effects meta-regression                   Number of obs  =         13
Method: REML                                     Residual heterogeneity:
                                                             tau2 =   .3132
                                                           I2 (%) =   92.22
                                                               H2 =   12.86
                                                 Wald chi2(0)   =         .
                                                 Prob > chi2    =         .

-------------------------------------------------------------------------------
    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+-----------------------------------------------------------------
       _cons |  -.7145323   .1797815    -3.97   0.000    -1.066898    -.362167
-------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(12) = 152.23  Prob > Q_res = 0.0000
```

Bubble plots after meta regress

A bubble plot is used after simple meta-regression with a continuous moderator to describe the relation between the effect size and the corresponding moderator.

It is used as a tool to assess how well the regression model fits the data and to potentially identify influential and outlying studies. The bubble plot is a scatterplot with the study-specific effect sizes plotted on the y axis and the moderator of interest from the meta-regression plotted on the x axis.

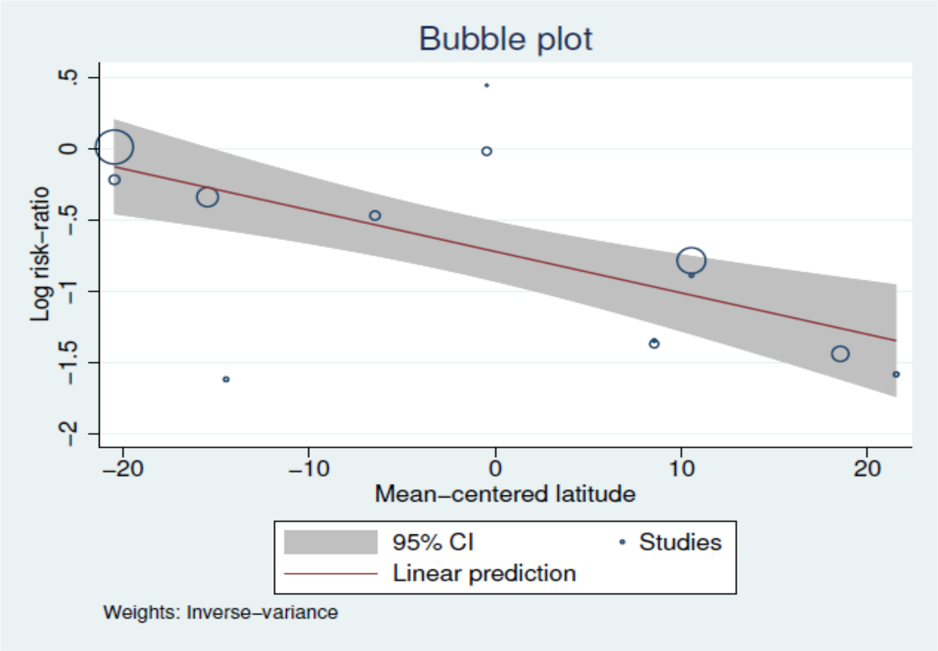
The sizes of the markers or “bubbles” are proportional to the precision of each study. The more precise (larger) the study, the larger the size of the bubble.

The predicted regression line and confidence bands are overlaid with the scatterplot.

.estat bubbleplot

produces bubble plots after simple meta-regression

Bubble plots



There appear to be a couple of outlying studies (see points in the bottom left and middle top sections of the plot), but their bubbles are very small, which suggests that their log risk-ratios estimates had small weights, relative to other studies, in the meta-regression.

Outlying studies with large bubbles may be a source of concern because of the large differences in their effect sizes compared with those from the other studies and because of the large impact they have on the regression results.

Publication bias

Publication bias or, more generally, reporting bias occurs when the studies selected for a scientific review are systematically different from all available relevant studies.

Publication bias is known in the meta-analysis literature as an association between the likelihood of a publication and the statistical significance of a study result.

The rise of systematic reviews for summarizing the results of scientific studies elevated the importance of acknowledging and addressing publication bias in research.

Publication bias typically arises when nonsignificant results are being underreported in the literature

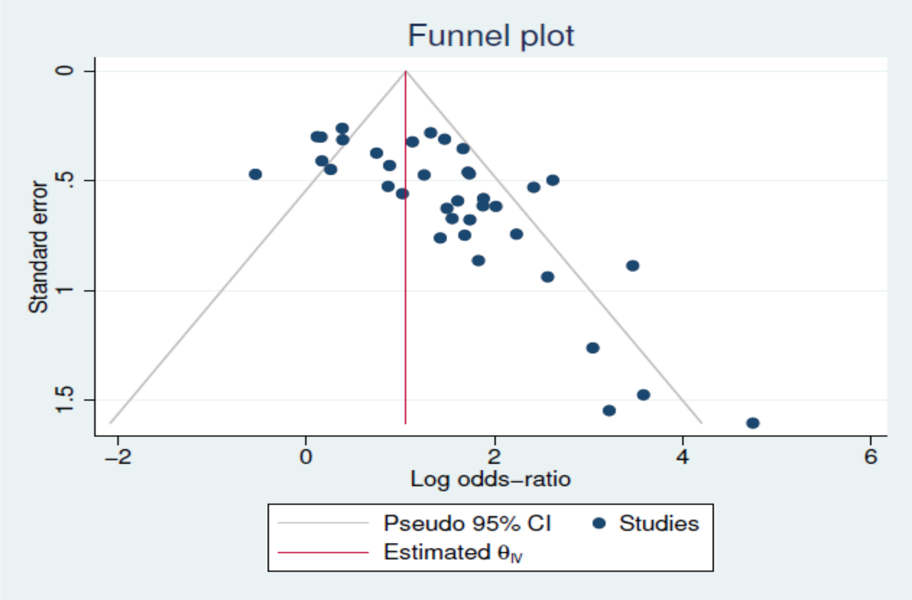
Funnel plots

The funnel plot is commonly used to explore publication bias . It is a scatterplot of the study-specific effect sizes versus measures of study precision.

In the absence of publication bias, the shape of the scatterplot should resemble a symmetric inverted funnel.

The funnel-plot asymmetry, however, may be caused by factors other than publication bias such as a presence of a moderator correlated with the study effect and study size or, more generally, the presence of substantial between-study heterogeneity.

Funnel plots



The funnel plot is clearly asymmetric with smaller, less precise studies—studies with larger standard errors—reporting larger effect sizes than the more precise studies.

This may suggest the presence of publication bias.

The plotted pseudo CI lines are not genuine CI limits, but they provide some insight into the spread of the observed effect sizes about the estimate of the overall effect size.

In the absence of publication bias and heterogeneity, we would expect the majority of studies to be randomly scattered within the CI region resembling an inverted funnel shape.

Notice: the default model used by meta funnel plot was the common-effect model with the inverse-variance method,

Tests for funnel plot asymmetry

Graphical evaluation of funnel plots is useful for data exploration but may be subjective when detecting the asymmetry.

Statistical tests provide a more formal evaluation of funnel-plot asymmetry.

These tests are also known as tests for small-study effects and historically, as tests for publication bias.

The tests are no longer referred to as “tests for publication bias” because, the presence of the funnel-plot asymmetry may not necessarily be attributed to publication bias, particularly in the presence of substantial between-study variability.

Tests for funnel plot asymmetry

Two types of tests for funnel-plot asymmetry are considered in the literature: regression-based tests and a nonparametric rank-based test.

Three regression-based tests and a nonparametric rank correlation test are available. For regression-based tests, you can include moderators to account for potential between-study heterogeneity.

These tests explore the relationship between the study specific effect sizes and study precision.

The presence of the funnel-plot asymmetry is declared when the association between the two measures is greater than what would have been observed by chance.

Test for small-study effects

Egger regression-based test (continuous data)

. meta bias, egger

Harbord regression-based test (binary data)

. meta bias, harbord

Peters regression-based test (binary data)

. meta bias, peters (supported only with effect size lnoratio)

Begg the nonparametric rank correlation test

. meta bias, begg (continuous data)

Examples of using meta bias (continuous data)

Recall the pupil IQ data described in Effects of teacher expectancy on pupil IQ of meta.

.use http://www.stata-press.com/data/r16/pupiliq.dta

.meta set stdmdiff se

In this data using meta set with variables stdmdiff and se specifying the effect sizes and their standard errors, respectively

. meta summarize

. meta forestplot

. meta funnelplot

Egger regression-based test (continuous data)

. meta bias, egger

```
  Effect-size label: Effect size
        Effect size: stdmdiff
          Std. err.: se

Regression-based Egger test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
            beta1 =      1.83
      SE of beta1 =     0.724
                z =      2.53
       Prob > |z| =    0.0115
```

The estimated slope, b1, is 1.83 with a standard error of 0.724, giving a test statistic of z = 2.53 and a p-value of 0.0115.

This means that there is some evidence of small-study effects.

subgroup-analysis on discrete variable

In the pupil IQ data, variable week1, which records whether teachers had prior contact with students for more than 1 week or for 1 week or less, to account for between-study heterogeneity. It explained most of the heterogeneity present among the effect sizes, with generally higher effect sizes in the low contact group.

Moderators that can explain a substantial amount of the heterogeneity should be included in the regression-based test as a covariate. By properly accounting for heterogeneity through the inclusion of week1, we can test for small-study effects due to reasons other than heterogeneity.

subgroup-analysis on discrete variable

.meta bias i.week1, egger

```
  Effect-size label: Effect size
        Effect size: stdmdiff
          Std. err.: se

Regression-based Egger test for small-study effects
Random-effects model
Method: REML
Moderators: week1

H0: beta1 = 0; no small-study effects
            beta1 =      0.30
      SE of beta1 =     0.729
                z =      0.41
       Prob > |z| =    0.6839
```

Now that we have accounted for heterogeneity through moderator week1, the Egger test statistic is 0.41 with a p-value of 0.6839. Therefore, we have strong evidence to say that the presence of small-study effects was the result of heterogeneity induced by teacher-student prior contact time.

Examples of using meta bias (binary data)

.use https://www.stata-press.com/data/r17/bcgset

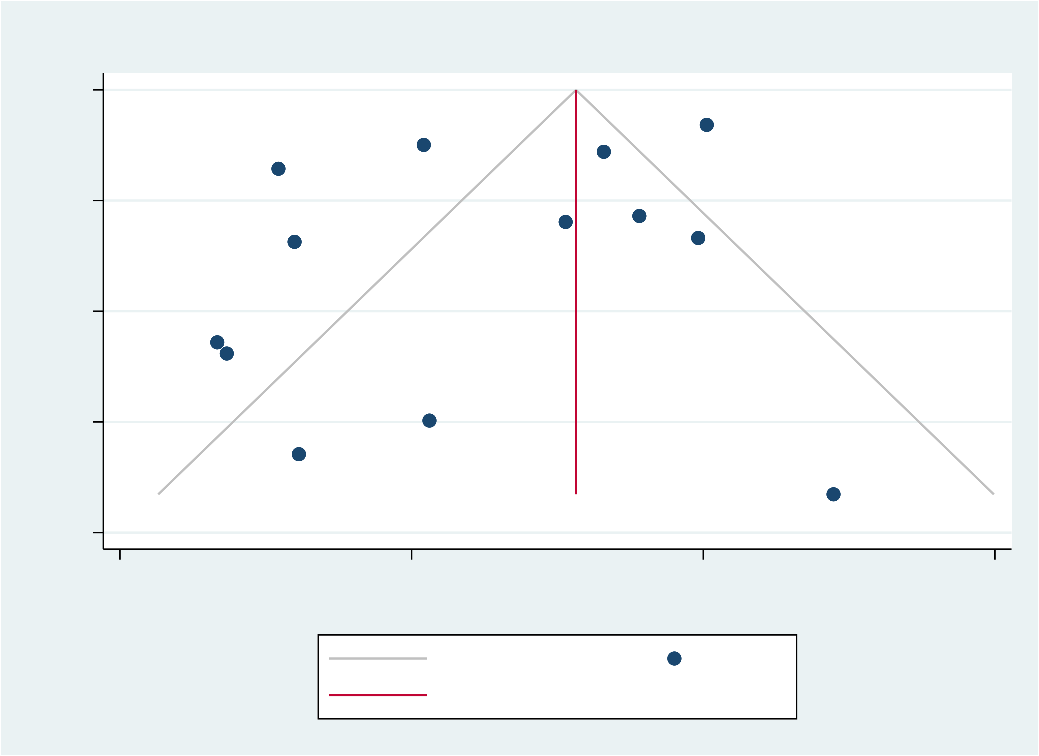
.meta bias,harb

```
H0: beta1 = 0; no small-study effects
            beta1 =      -0.82
      SE of beta1 =      0.973
                z =      -0.84
       Prob > |z| =     0.4011
```

The estimated slope, b1, is -0.82 with a standard error of 0.973, giving a test statistic of z = -0.84 and a p-value of 0.4011.

This means that there is not evidence of small-study effects.

Funnel Plot



The trim and fill method

Tests for funnel-plot asymmetry are useful for detecting publication bias but are not able to estimate the impact of this bias on the final meta-analysis results.

The nonparametric trim-and-fill method provides a way to assess the impact of missing studies because of publication bias on the meta-analysis.

It evaluates the amount of potential bias present in meta-analysis and its impact on the final conclusion.

This method is typically used as a sensitivity analysis to the presence of publication bias.

The trim and fill example

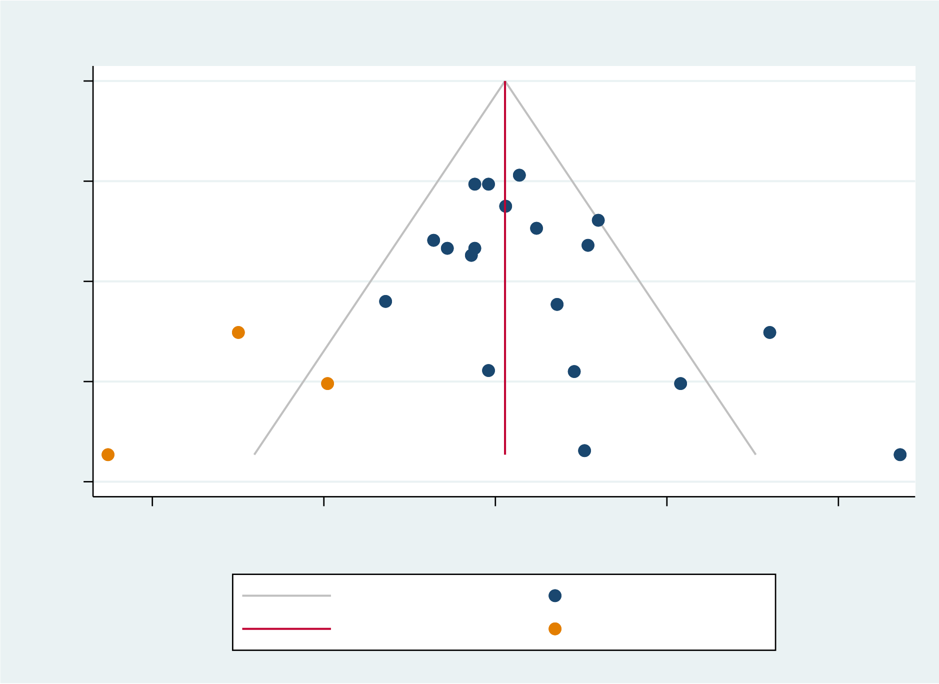
.use http://www.stata-press.com/data/r16/pupiliq.dta

.meta trimfill

```
  Effect-size label: Effect size
        Effect size: stdmdiff
          Std. err.: se

Nonparametric trim-and-fill analysis of publication bias
Linear estimator, imputing on the left

Iteration                            Number of studies =     22
  Model: Random-effects                       observed =     19
 Method: REML                                 imputed =      3

Pooling
  Model: Random-effects
 Method: REML
```

Studies	Effect size	[95% conf.	interval]
Observed	0.084	-0.018	0.185
Observed + Imputed	0.028	-0.117	0.173

.meta trimfill, funnel



The trim and fill interpretation

The mean effect size based on the 19 observed studies is 0.0.084 with a 95% CI of [-0.018; 0.185].

Three hypothetical studies, are estimated to be missing and are imputed. If these three studies were included in the meta-analysis, the funnel plot would be more symmetrical.

After imputing the studies, we obtain an updated estimate (based on the 22 studies, observed plus imputed) of the mean effect size of 0.028 with a 95% CI [-0.117; 0.173].

Galbraith Plot (heterogeneity)

This plot is useful for assessing heterogeneity of the studies and for detecting potential outliers. It may also be an alternative to forest plots for summarizing meta-analysis results when there are many studies.

. meta galbraithplot

use https://www.stata-press.com/data/r17/bcgset

(Efficacy of BCG vaccine against tuberculosis; set with -meta esize-)

This data is in meta format.

We can use these command before galbraithplot

.meta summarize

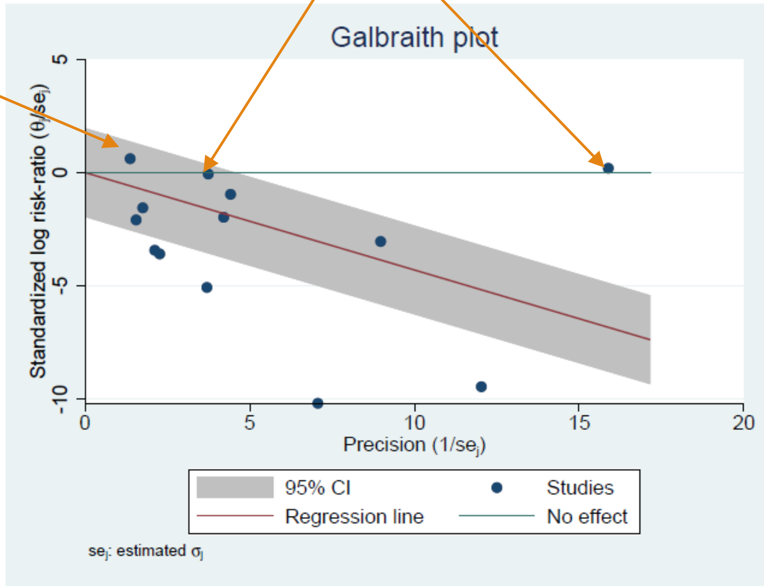
. meta forestplot

Galbraith Plot Out Put

```
Effect-size label: Log risk-ratio
      Effect size: _meta_es
        Std. err.: _meta_se
            Model: Common effect
           Method: Inverse-variance
```

The log risks for these trials are similar in the two groups

the risk in the treatment group is higher



Galbraith Plot Out Put Interpretation

The navy circles form a scatterplot of the study-specific effect size (standardized log risk-ratios) against study precisions. Studies that are close to the y axis have low precision. Precision of studies increases as you move toward the right on the x axis.

The reference green line (y = 0) represents the “no-effect” line. That is, the log risks (or risks) in the treatment and control groups for the trials on the line are either the same or very similar. There are two trials that are on the line in our example: one is a large trial, and the other one is a small trial. The log risks for these trials are similar in the two groups, and the corresponding log risk-ratios are close to zero.

If a circle is above the reference line, the risk in the treatment group is higher than the risk in the control group for that study. Conversely, if a circle is below the line, the risk in the treatment group is lower than the risk in the control group. In our example, one trial is above the reference line, suggesting that the risk in the treatment group is higher, but this is an imprecise trial. The remaining trials are below the line, suggesting that the risk is lower in the treatment group.

Studies that fall above the regression line have effect-size estimates larger than the overall effect size, and those falling below the line have estimates that are smaller than the overall effect size.

In the absence of substantial heterogeneity, we expect around 95% of the studies to lie within the 95% CI region (shaded area). In our example, there are 6 trials out of 13 that are outside of the CI region. We should suspect the presence of heterogeneity in these data.

L’ABBE PLOT (binary data)

L’Abb´e plots for a meta-analysis that compares the binary outcomes of two groups. These plots are useful for assessing heterogeneity and comparing study-specific event rates in the two groups after meta esize.

. meta labbeplot

Consider the declared version of the BCG dataset, bcgset.dta,

use https://www.stata-press.com/data/r17/bcgset

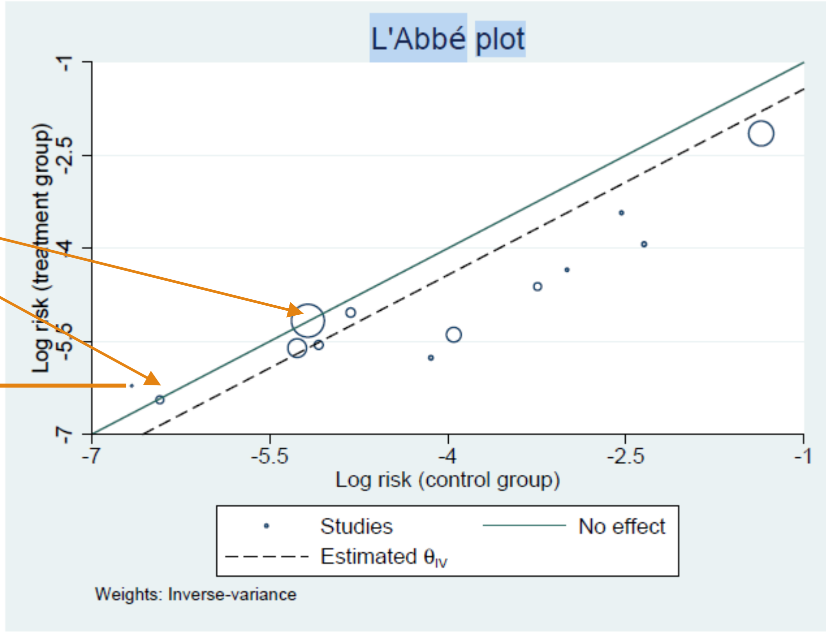
(Efficacy of BCG vaccine against tuberculosis; set with –met a esize-)

L'ABBE PLOT Out Put

```
Effect-size label: Log risk-ratio
      Effect size: _meta_es
        Std. err.: _meta_se
     Summary data: npost nnegt nposc nnegc
            Model: Common effect
           Method: Inverse-variance
```

The log risks for these trials are very similar in the two groups

the risk in the treatment group is higher



L’ABBE PLOT Out Put Interpretation

The treatment-group log risk is on the y axis, and the control-group log risk is on the x axis. The sizes of the plotted markers (circles) are proportional to the precision of the trials. Large circles represent more precise, larger trials, whereas small circles represent less precise, smaller trials.

The solid reference line ($y = x$) represents the “no-effect” line. That is, the log risks (or risks) in the two groups for the trials on the line are either the same or very similar. There are two trials that are on the line in our example: one is a large trial, the other one is a small trial. The log risks for these trials are very similar in the two groups, and the corresponding log risk-ratios are close to zero.

L'ABBE PLOT Out Put Interpretation

If a circle is above the reference line, the risk in the treatment group is higher than the risk in the control group for that study. Conversely, if a circle is below the line, the risk in the treatment group is lower than the risk in the control group. In our example, one trial is above the reference line, suggesting that the risk in the treatment group is higher, but this is a very small trial. The remaining trials are below the line, suggesting that the risk is lower in the treatment group. However, the trials demonstrating large differences between the groups are also smaller (less precise) trials.

The dashed line is the overall effect-size line. The intercept of this line equals the estimate of the overall effect size, which is the overall log risk-ratio in our example. The actual estimate of the overall effect size is not important in the L'Abb´e plot. What is important is whether the circles follow the effect-size line or deviate from it.

When the circles deviate from the effect-size line greatly, this may be a sign of study heterogeneity.

In our example, there are at least five trials that are far away from the effect-size line. We should suspect the presence of heterogeneity in these data.

Cumulative Meta Analysis

Cumulative meta-analysis performs multiple meta-analyses, where each analysis is produced by adding one study at a time. It is useful to identify various trends in the overall effect sizes. For example, when the studies are ordered chronologically, one can determine the point in time of the potential change in the direction or significance of the effect size.

meta summarize, cumulative()

meta forestplot, cumulative()

. use https://www.stata-press.com/data/r17/strepto

(Effect of streptokinase after a myocardial infarction)

.describe

.meta esize ndeadt nsurvt ndeadc nsurvc, studylabel(studyplus) common

. meta forestplot, cumulative(year) or crop(0.5)

Cumulative Meta Analysis Interpretation

The cumulative meta-analysis forest plot displays the overall effect-size estimates and the corresponding CIs computed for the first study, for the first two studies, for the first three studies, and so on. The point estimates are represented by green circles, and the CIs are represented by the CI lines.

The “+” sign in front of the study label we used for this analysis (variable studyplus) indicates that each subsequent study is being added to the previous ones for each analysis. In addition to the ordered values of the specified variable of interest (year in our example), the plot also displays the p-values corresponding to the tests of significance of the computed overall effect sizes.

Notice that the first two odds-ratio estimates (and their lower CI limits) are smaller than 0.5. Because we used the crop(0.5 .) option, their values are not displayed on the graph. Instead, the arrowheads are displayed at the lower ends of the CI lines to indicate that the lower limits and the effect-size estimates are smaller than 0.5.

Leave one out Meta Analysis

The leave-one-out meta-analysis also performs multiple meta analysis; however, in this case, each analysis is produced by excluding a single study. It is quite common that studies yield effect sizes that are relatively exaggerated. Their presence in the meta analysis may distort the overall results, and it is of great importance to identify such studies for further examination. The leave-one-out meta-analysis is a useful tool to investigate the influence of each study on the overall effect size estimate.

```
.meta summarize, leaveoneout
```

```
.meta forestplot, leaveoneout
```

Sensitivity meta-analysis

We can perform sensitivity analysis to explore the impact of the various levels of heterogeneity on the regression results. let's fit a meta-regression assuming that the residual heterogeneity statistic I2 equals 90%.

. use https://www.stata-press.com/data/r17/bcgset

. meta regress latitude_c, i2(90)

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                  Number of obs  =         13
Method: User-specified I2                       Residual heterogeneity:
                                                            tau2 =    .3176
                                                          I2 (%) =    90.00
                                                              H2 =    10.00
                                                Wald chi2(1)   =       4.89
                                                Prob > chi2    =     0.0269
```

_meta_es	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
latitude_c	-.0277589	.0125474	-2.21	0.027	-.0523514	-.0031664
_cons	-.7443082	.1812664	-4.11	0.000	-1.099584	-.3890326

```
Test of residual homogeneity: Q_res = chi2(11) = 30.73   Prob > Q_res = 0.0012
```

Let's now fit a meta-regression assuming the between-study variance of 0.01.

.meta regress latitude_c, tau2(0.01)

The specified value of tau2 corresponds to the I2 value of 22.08%. The coefficient estimate is now -0.0295 with a standard error of 0.0039.

In both sensitivity analyses, latitude c remained a statistically significant moderator for the log risk-ratios.

```
  Effect-size label: Log risk-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                     Number of obs  =        13
Method: User-specified tau2                        Residual heterogeneity:
                                                               tau2 =     .01
                                                             I2 (%) =   22.08
                                                                 H2 =    1.28
                                                   Wald chi2(1)   =     57.62
                                                   Prob > chi2    =    0.0000

    _meta_es | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
  latitude_c |  -.0295601   .0038942    -7.59   0.000    -.0371926   -.0219277
       _cons |  -.6767043   .0617892   -10.95   0.000    -.7978089   -.5555998

Test of residual homogeneity: Q_res = chi2(11) = 30.73   Prob > Q_res = 0.0012
```