Performing multivariate meta-analysis in Stata

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May 24, 2022

Overview

- What is multivariate meta-analysis?
- Perform multivariate meta-analysis in Stata
- Obtain fitted values and create diagnostic plots
- Perform sensitivity analysis

Introduction

Univariate meta-analysis

- Meta-analysis is a statistical technique for combining the results from several similar studies.
- The goal is to provide a single estimate of the effect of interest.
- If results vary widely across studies, the goal is then to understand the inconsistencies in the results.

Univariate meta-analysis data

```
. list study es se studylab in 1/5
```

	study	es	se	studylab
1.	1	1.4796	.93426213	Smith et al. (1984)
2.	2	.99909748	.9856864	Jones and Miller (1989)
3.	3	1.2720385	.43128775	Johnson et al. (1991)
4.	4	1.0008144	.12801226	Brown et al. (1995)
5.	5	1.1788405	.87014702	Clark and Thomas (1998)

Multivariate meta-analysis

- Multivariate meta-analysis extends the application of meta-analysis to scenarios where each study reports multiple, dependent effect sizes.
- As with univariate meta-analysis, our goal is to synthesize the results from the studies; if results vary widely across studies, we aim to explain the heterogeneity.

Multivariate meta-analysis data

- Multivariate meta-analysis data can arise when you are comparing multiple outcomes across two groups.
  - Suppose our treatment group is on a low-carb diet, and we want to compare weight loss, blood pressure, and cholesterol across the treatment and control groups.
  - The three measures are compared across the same subjects, so the effect sizes are dependent.

Multivariate meta-analysis data

- Multivariate meta-analysis data can also arise when you are comparing different treatment groups with a control group.
  - For example, you might look at the difference in the average weight loss for individuals on a keto diet, those undergoing intermittent fasting, and those on a high protein diet, compared with a control group.
  - The differences would be correlated across groups because we are comparing them with the same control group.

Analyzing multivariate data

Traditional methods used to analyze these data:

- Perform univariate meta-analysis for each outcome.
  - This would ignore any dependence between the effect sizes, leading to biased results and less precise estimates.
- Combine the effect sizes for each study into one effect size. Then, perform univariate meta-analysis on this combined effect size.
  - This method results in loss of information.
  - Summarizing changes in weight loss, blood pressure, and cholesterol with a single value may be hard to interpret.

Multivariate meta-analysis

- With multivariate meta-analysis we can use the information we have about the correlation of the outcomes to get a more precise estimate of the effect sizes.
- If the studies are heterogeneous, we can try to determine the reason for the between-study heterogeneity by including moderators and performing multivariate meta-regression.

Example 1

Periodontal data

- We have data from Antczak-Bouckoms et al. (1993) comparing the effectiveness of two treatments for treating periodontal disease.

  Treatment 1: Surgical

  Treatment 2: Nonsurgical

- We have two outcomes (effect sizes)

  Y1: Mean improvement from baseline in probing depth (mm)

  Y2: Mean improvement in attachment level (mm)

Probing depth and attachment levels

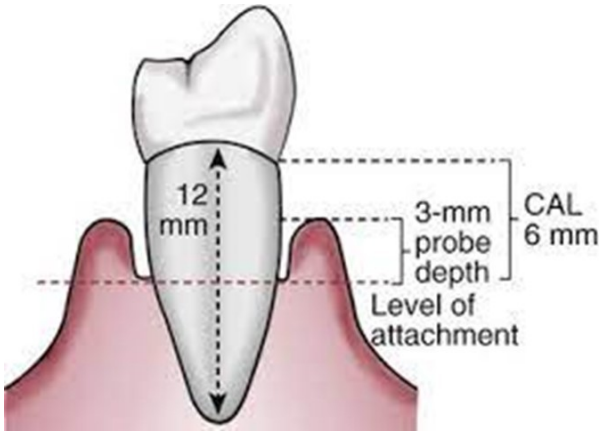


Figure: Image of probe depth and attachment level. *Pocket Dentistry* https://pocketdentistry.com/7-periodontal-diseases. Accessed 08 Feb. 2022.

Periodontal data

```
. describe
Contains data from https://www.stata-press.com/data/r17/periodontal.dta
 Observations:             5                  Treatment of moderate periodontal disease
    Variables:            10                  13 Jan 2021 18:11
                                              (_dta has notes)
```

Variable name	Storage type	Display format	Value label	Variable label
trial	str23	%23s		Trial label
pubyear	byte	%9.0g		Publication year centered at 1983
depth	float	%6.2f		Mean improvement in probing depth (mm)
attachment	float	%6.2f		Mean improvement in attachment level (mm)
v_d	float	%6.4f		Variance of depth
cov_da	float	%6.4f		Covariance of depth and attachment
v_a	float	%6.4f		Variance of attachment
se_d	double	%10.0g		Standard error of depth
se_a	double	%10.0g		Standard error of attachment
study	float	%9.0g		Study number

```
Sorted by:
     Note: Dataset has changed since last saved.
```

Periodontal data

```
. list study depth v_d attachment v_a cov_da, ab(10)
```

	study	depth	v_d	attachment	v_a	cov_da
1.	1	0.47	0.0075	-0.32	0.0077	0.0030
2.	2	0.20	0.0057	-0.60	0.0008	0.0009
3.	3	0.40	0.0021	-0.12	0.0014	0.0007
4.	4	0.26	0.0029	-0.31	0.0015	0.0009
5.	5	0.56	0.0148	-0.39	0.0304	0.0072

Multivariate meta-analysis models

- Fixed effects: We assume all heterogeneity between study effect sizes is due to sampling error.
- Random effects: We assume some of the variability is due to sampling error and a portion is due to actual differences in the true effect size.
    - For example, we could observe differences in the risk ratio if one study had many subjects with poor dental hygiene (a risk factor for periodontal disease) and another study mainly had subjects with great dental hygiene.

Multivariate meta-regression in Stata

- Fixed-effects

  `meta mvregress` *depvars* [`=` *moderators*]`,` *wcovspec* `fixed`

- Random-effects

  `meta mvregress` *depvars* [`=` *moderators*]`,` *wcovspec*
  [`random(`*rspec*`)`]

- *wcovspec* refers to the relationship between the outcomes, within each study. You'll specify either of the following:
  - the variance of each outcome and the covariance of the outcomes
  - the standard error for each outcome and the correlation between the outcomes
- Unlike with other `meta` commands, our data do not need to be `meta set` to use `meta mvregress`.

Random-effects models

- `random(`*remethod* [`, covariance(`*recov*`) se(`*seadj*`)`]
- We can specify the type of estimator (*remethod*) and the structure of the covariance matrix (*recov*) and apply adjustments to the standard errors (*seadj*):
  - *remethod* can be restricted maximum likelihood, maximum likelihood, or the Jackson-White-Riley method.
  - *recov* can be `unstructured`, `independent`, `exchangeable`, `identity`, or `fixed`.
  - *seadj* can be the Jackson-Riley adjustment or the truncated Jackson-Riley adjustment.
- The default is `random(reml, covariance(unstructured))`.

Multivariate meta-analysis

```
. meta mvregress depth attachment, wcovvariables(v_d cov_da v_a) nolog
Multivariate random-effects meta-analysis       Number of obs     =         10
Method: REML                                    Number of studies =          5
                                                Obs per study:
                                                              min =          2
                                                              avg =        2.0
                                                              max =          2
                                                Wald chi2(0)      =          .
Log restricted-likelihood = 2.0823276           Prob > chi2       =          .
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
depth						
_cons	.3534282	.0588486	6.01	0.000	.238087	.4687694
attachment						
_cons	-.3392152	.0879051	-3.86	0.000	-.5115061	-.1669243

Test of homogeneity: Q_M = chi2(8) = 128.23 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(depth)	.1083191
sd(attach~t)	.1806968
corr(depth,attach~t)	.6087987

Heterogeneity

```
. estat heterogeneity

Method: Cochran
Joint:
  I2 (%) = 93.76
      H2 = 16.03

Method: Jackson-White-Riley
depth:
  I2 (%) = 76.42
       R =  2.06

attachment:
  I2 (%) = 95.50
       R =  4.71

Joint:
  I2 (%) = 88.66
       R =  2.97
```

Multivariate meta-regression

```
. meta mvregress depth attachment = pubyear, wcovvariables(v_d cov_da v_a) nolog
Multivariate random-effects meta-regression     Number of obs      =         10
Method: REML                                    Number of studies  =          5
                                                Obs per study:
                                                              min  =          2
                                                              avg  =        2.0
                                                              max  =          2
                                                Wald chi2(2)       =       0.40
Log restricted-likelihood = -3.5399567          Prob > chi2        =     0.8197
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
depth						
pubyear	.0048615	.0218511	0.22	0.824	-.0379658	.0476888
_cons	.3587569	.07345	4.88	0.000	.2147975	.5027163
attachment						
pubyear	-.0115367	.0299635	-0.39	0.700	-.070264	.0471907
_cons	-.3357368	.0979979	-3.43	0.001	-.5278091	-.1436645

Test of homogeneity: Q_M = chi2(6) = 125.76 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(depth)	.1429917
sd(attach~t)	.2021314
corr(depth,attach~t)	.561385

Multivariate meta-analysis

```
. meta mvregress depth attachment, wcovvariables(v_d cov_da v_a) nolog
Multivariate random-effects meta-analysis       Number of obs     =         10
Method: REML                                    Number of studies =          5
                                                Obs per study:
                                                              min =          2
                                                              avg =        2.0
                                                              max =          2
                                                Wald chi2(0)      =          .
Log restricted-likelihood = 2.0823276           Prob > chi2       =          .
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
depth						
_cons	.3534282	.0588486	6.01	0.000	.238087	.4687694
attachment						
_cons	-.3392152	.0879051	-3.86	0.000	-.5115061	-.1669243

Test of homogeneity: Q_M = chi2(8) = 128.23 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(depth)	.1083191
sd(attach~t)	.1806968
corr(depth,attach~t)	.6087987

Making adjustments

- The `REML` estimator assumes the random effects are normally distributed; we can relax this assumption with the Jackson-White-Riley estimator.
- Additionally, we'll apply the Jackson-Riley adjustment (Jackson and Riley 2014) to the standard errors of the coefficients.
  - This adjustment provides more accurate estimates of the standard errors when working with a small number of studies.

Multivariate meta-analysis

```
. meta mvregress depth attachment, wcovvariables(v_d cov_da v_a) random(jwriley, se(jriley))
Multivariate random-effects meta-analysis       Number of obs      =         10
Method: Jackson-White-Riley                     Number of studies  =          5
SE adjustment: Jackson-Riley                    Obs per study:
                                                              min  =          2
                                                              avg  =        2.0
                                                              max  =          2
                                                F(0,      8.00)    =          .
                                                Prob > F           =          .
```

	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
depth						
_cons	.352096	.0596134	5.91	0.000	.2146271	.4895648
attachment						
_cons	-.3380344	.1062918	-3.18	0.013	-.5831438	-.0929251

Test of homogeneity: Q_M = chi2(8) = 128.23 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(depth)	.1210675
sd(attach~t)	.240236
corr(depth,attach~t)	.7393752

Obtaining fitted values

- With `predict`, you can obtain the best linear unbiased prediction of the random effects and their standard errors, as well as predictions of the residuals and standardized residuals.
- Below, we obtain the fitted values for each outcome:

```
. predict double fit1, fitted depvar(depth)
. predict double fit2, fitted depvar(attachment)
```

Diagnostic plot

- Below, we plot the fitted values against the observed values.
- Graph for outcome 1:

```
. twoway (scatter fit1 depth, mlabel(trial))
  (function y = x), name(graph1)
```

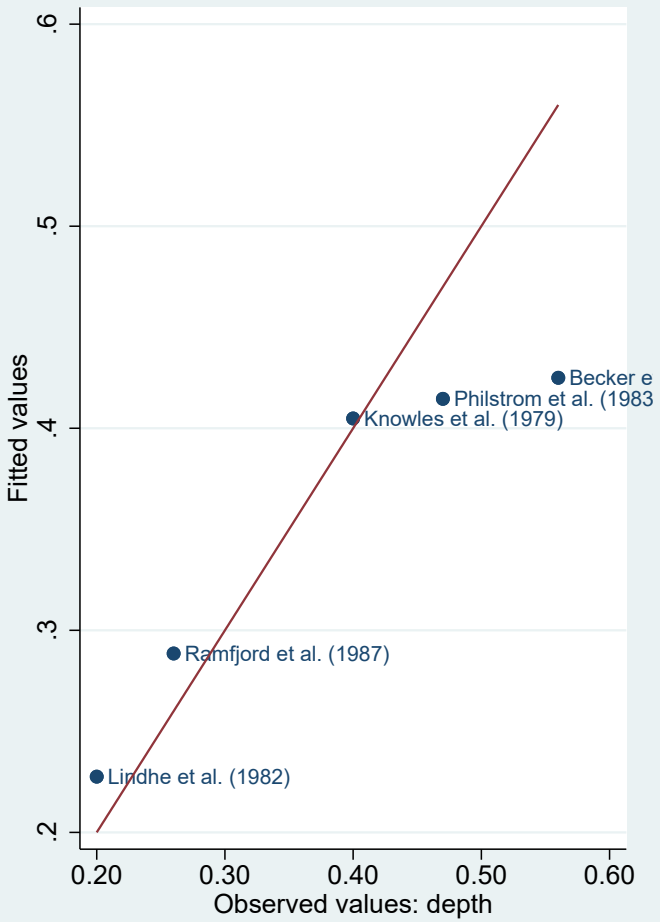
- Graph for outcome 2:

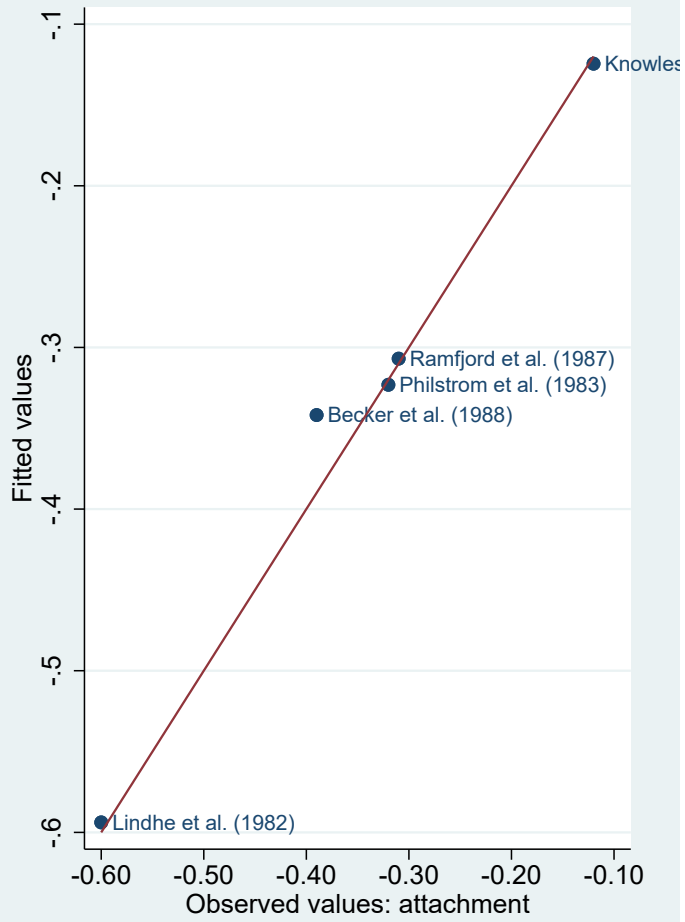
```
. twoway (scatter fit2 attach, mlabel(trial))
  (function y = x), name(graph2)
```

- Combine the graphs:

```
. graph combine graph1 graph2
```

Assessing goodness of fit





Example 2

Data on smoking cessation

- We have data from Fiore et al. (1996) on the impact of four interventions on smoking cessation
  - **a**: no contact
  - **b**: self-help
  - **c**: individual counseling
  - **d**: group counseling
- Our effect sizes are the log odds-ratios comparing intervention types b, c, and d with intervention a

Intervention types for smoking cessation

```
. webuse smokecess, clear
(Smoking cessation interventions)
. describe y* v*
```

Variable name	Storage type	Display format	Value label	Variable label
yb	double	%9.0g		Log-odds ratio (b vs a)
yc	double	%9.0g		Log-odds ratio (c vs a)
yd	double	%9.0g		Log-odds ratio (d vs a)
vbb	double	%9.0g		Variance of yb
vbc	double	%9.0g		Covariance of yb and yc
vbd	double	%9.0g		Covariance of yb and yd
vcc	double	%9.0g		Variance of yc
vcd	double	%9.0g		Covariance of yc and yd
vdd	double	%9.0g		Variance of yd

Trivariate meta-analysis

```
. meta mvregress yb yc yd, wcovvariables(vbb vbc vbd vcc vcd vdd) random(mle) nolog noheader
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.2092245	.1646492	1.27	0.204	-.1134821	.5319311
yc						
_cons	.6723171	.1957326	3.43	0.001	.2886881	1.055946
yd						
_cons	.7284868	.2693173	2.70	0.007	.2006345	1.256339

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(yb)	.1525079
sd(yc)	.712901
sd(yd)	.422447
corr(yb,yc)	.7160185
corr(yb,yd)	.9915944
corr(yc,yd)	.6196787

Heterogeneity

```
. estat heterogeneity

Method: Cochran
Joint:
  I2 (%) = 86.29
      H2 =  7.29

Method: Jackson-White-Riley
yb:
  I2 (%) = 41.45
       R =  1.31

yc:
  I2 (%) = 90.89
       R =  3.31

yd:
  I2 (%) = 51.32
       R =  1.43

Joint:
  I2 (%) = 69.05
       R =  1.80
```

Assess joint heterogeneity

```
. estat heterogeneity, jwriley(yb yd)

Method: Jackson-White-Riley
yb yd:
  I2 (%) = 45.10
       R =  1.35
```

Trivariate meta-analysis

```
. meta mvregress yb yc yd, wcovvariables(vbb vbc vbd vcc vcd vdd) random(mle) nolog noheader
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.2092245	.1646492	1.27	0.204	-.1134821	.5319311
yc						
_cons	.6723171	.1957326	3.43	0.001	.2886881	1.055946
yd						
_cons	.7284868	.2693173	2.70	0.007	.2006345	1.256339

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Unstructured:	
sd(yb)	.1525079
sd(yc)	.712901
sd(yd)	.422447
corr(yb,yc)	.7160185
corr(yb,yd)	.9915944
corr(yc,yd)	.6196787

Missing values

```
. misstable pattern yb yd, frequency
  Missing-value patterns
    (1 means complete)

                |  Pattern
  Frequency     |  1  2
----------------+-------
          2     |  1  1
                |
         14     |  0  0
          4     |  0  1
          4     |  1  0
----------------+-------
         24     |
Variables are  (1) yb  (2) yd
```

Covariance structures

$$\texttt{unstructured} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ \sigma_{21} & \sigma_{22} & \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix}$$

$$\texttt{independent} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ 0 & \sigma_{22} & \\ 0 & 0 & \sigma_{33} \end{bmatrix}$$

$$\texttt{exchangeable} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ \sigma_{21} & \sigma_{11} & \\ \sigma_{21} & \sigma_{21} & \sigma_{11} \end{bmatrix}$$

$$\texttt{identity} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ 0 & \sigma_{11} & \\ 0 & 0 & \sigma_{11} \end{bmatrix}$$

Independent covariance structure

```
. meta mvregress y*, wcovvariables(v*) random(mle, covariance(independent)) nolog
Multivariate random-effects meta-analysis       Number of obs      =         31
Method: ML                                      Number of studies  =         24
                                                Obs per study:
                                                              min  =          1
                                                              avg  =        1.3
                                                              max  =          3
                                                Wald chi2(0)       =          .
Log likelihood = -52.106793                     Prob > chi2        =          .
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.1472931	.1345138	1.10	0.274	-.1163492	.4109354
yc						
_cons	.6486399	.1931684	3.36	0.001	.2700368	1.027243
yd						
_cons	.6631891	.2435873	2.72	0.006	.1857668	1.140611

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Independent:	
sd(yb)	.000179
sd(yc)	.6942969
sd(yd)	.0927756

More missing values

```
. misstable pattern yb, frequency
  Missing-value patterns
    (1 means complete)

             |  Pattern
   Frequency |  1
-------------+-------------
           6 |  1
          18 |  0
-------------+-------------
          24 |
  Variables are  (1) yb
```

Covariance structures

$$\texttt{unstructured} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ \sigma_{21} & \sigma_{22} & \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix}$$

$$\texttt{independent} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ 0 & \sigma_{22} & \\ 0 & 0 & \sigma_{33} \end{bmatrix}$$

$$\texttt{exchangeable} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ \sigma_{21} & \sigma_{11} & \\ \sigma_{21} & \sigma_{21} & \sigma_{11} \end{bmatrix}$$

$$\texttt{identity} \quad \Sigma = \begin{bmatrix} \sigma_{11} & & \\ 0 & \sigma_{11} & \\ 0 & 0 & \sigma_{11} \end{bmatrix}$$

Identity covariance structure

```
. meta mvregress y*, wcovvariables(v*) random(mle, covariance(identity)) nolog
Multivariate random-effects meta-analysis       Number of obs      =        31
Method: ML                                      Number of studies  =        24
                                                Obs per study:
                                                              min  =         1
                                                              avg  =       1.3
                                                              max  =         3
                                                Wald chi2(0)       =         .
Log likelihood = -54.501897                     Prob > chi2        =         .
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.3671705	.3168396	1.16	0.247	-.2538237	.9881648
yc						
_cons	.6742327	.1759043	3.83	0.000	.3294666	1.018999
yd						
_cons	.8642315	.3964733	2.18	0.029	.0871582	1.641305

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
Identity:	
sd(yb yc yd)	.579771

Sensitivity analysis

Sensitivity analysis

- Sensitivity analysis may be of interest when you have a lot of missing observations or when the number of observations is small relative to the number of parameters to be estimated.

```
. misstable pattern yb yd, frequency
  Missing-value patterns
    (1 means complete)

                |  Pattern
  Frequency     |  1  2
----------------+-------
          2     |  1  1
                |
         14     |  0  0
          4     |  0  1
          4     |  1  0
----------------+-------
         24     |
Variables are  (1) yb  (2) yd
```

Sensitivity analysis

- To perform sensitivity analysis, we will fit the model setting the correlation between the random effects of **yb** and **yc** to 0, 0.4, and 0.8.
- We will assume that the random effect associated with **yd** is uncorrelated with the random-effects of **yb** and **yc**.
- Then, we will create a table with all three sets of estimation results.

Correlation matrices

```
. matrix list Sigma1 // no correlation
symmetric Sigma1[3,3]
    c1  c2  c3
r1   1
r2   0   1
r3   0   0   1
. matrix list Sigma2 // moderate correlation (0.4)
symmetric Sigma2[3,3]
    c1  c2  c3
r1   1
r2  .4   1
r3   0   0   1
. matrix list Sigma3 // high correlation (0.8)
symmetric Sigma3[3,3]
    c1  c2  c3
r1   1
r2  .8   1
r3   0   0   1
```

No correlation

```
. meta mvregress y*, wcovvariables(v*) random(mle, covariance(fixed(Sigma1))) noheader
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.4293913	.502528	0.85	0.393	-.5555455	1.414328
yc						
_cons	.7629462	.2739889	2.78	0.005	.2259379	1.299955
yd						
_cons	1.028532	.5979445	1.72	0.085	-.1434175	2.200482

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
User-specified Sigma1:	
sd(yb)	1
sd(yc)	1
sd(yd)	1
corr(yb,yc)	0
corr(yb,yd)	0
corr(yc,yd)	0

```
. estimates store corr0
```

Moderate correlation

```
. meta mvregress y*, wcovvariables(v*) random(mle, covariance(fixed(Sigma2))) noheader
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.4718864	.4776655	0.99	0.323	-.4643209	1.408094
yc						
_cons	.7524677	.2714654	2.77	0.006	.2204053	1.28453
yd						
_cons	1.039496	.6030185	1.72	0.085	-.1423987	2.22139

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
User-specified Sigma2:	
sd(yb)	1
sd(yc)	1
sd(yd)	1
corr(yb,yc)	.4
corr(yb,yd)	0
corr(yc,yd)	0

```
. estimates store corr4
```

High correlation

```
. meta mvregress y*, wcovvariables(v*) random(mle, covariance(fixed(Sigma3))) noheader
```

	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
yb						
_cons	.5656914	.4182064	1.35	0.176	-.2539781	1.385361
yc						
_cons	.7299476	.2659099	2.75	0.006	.2087738	1.251121
yd						
_cons	1.05668	.6067065	1.74	0.082	-.1324433	2.245803

Test of homogeneity: Q_M = chi2(28) = 204.22 Prob > Q_M = 0.0000

Random-effects parameters	Estimate
User-specified Sigma3:	
sd(yb)	1
sd(yc)	1
sd(yd)	1
corr(yb,yc)	.8
corr(yb,yd)	0
corr(yc,yd)	0

```
. estimates store corr8
```

Estimation results

```
. estimates table corr0 corr4 corr8,
  keep(yb:_cons yc:_cons yd:_cons) b(%8.3f) se(%8.3f)
```

Variable	corr0	corr4	corr8
yb			
_cons	0.429	0.472	0.566
	0.503	0.478	0.418
yc			
_cons	0.763	0.752	0.730
	0.274	0.271	0.266
yd			
_cons	1.029	1.039	1.057
	0.598	0.603	0.607

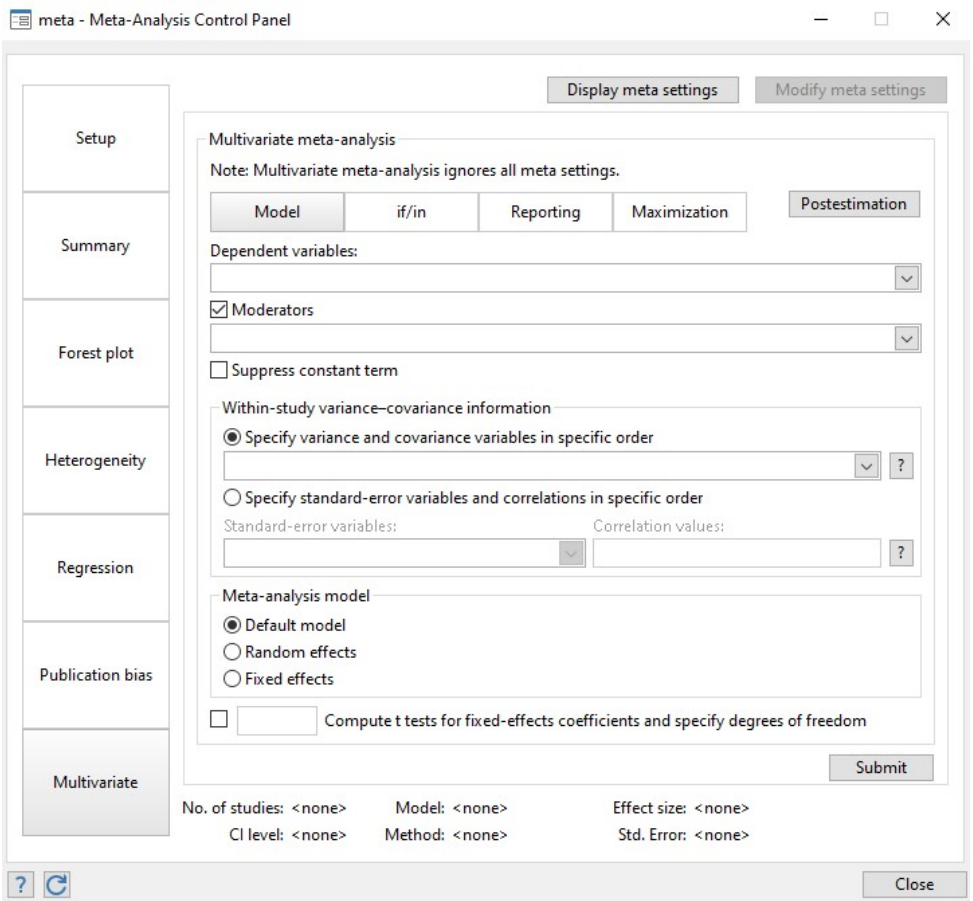
Legend: b/se

Summary

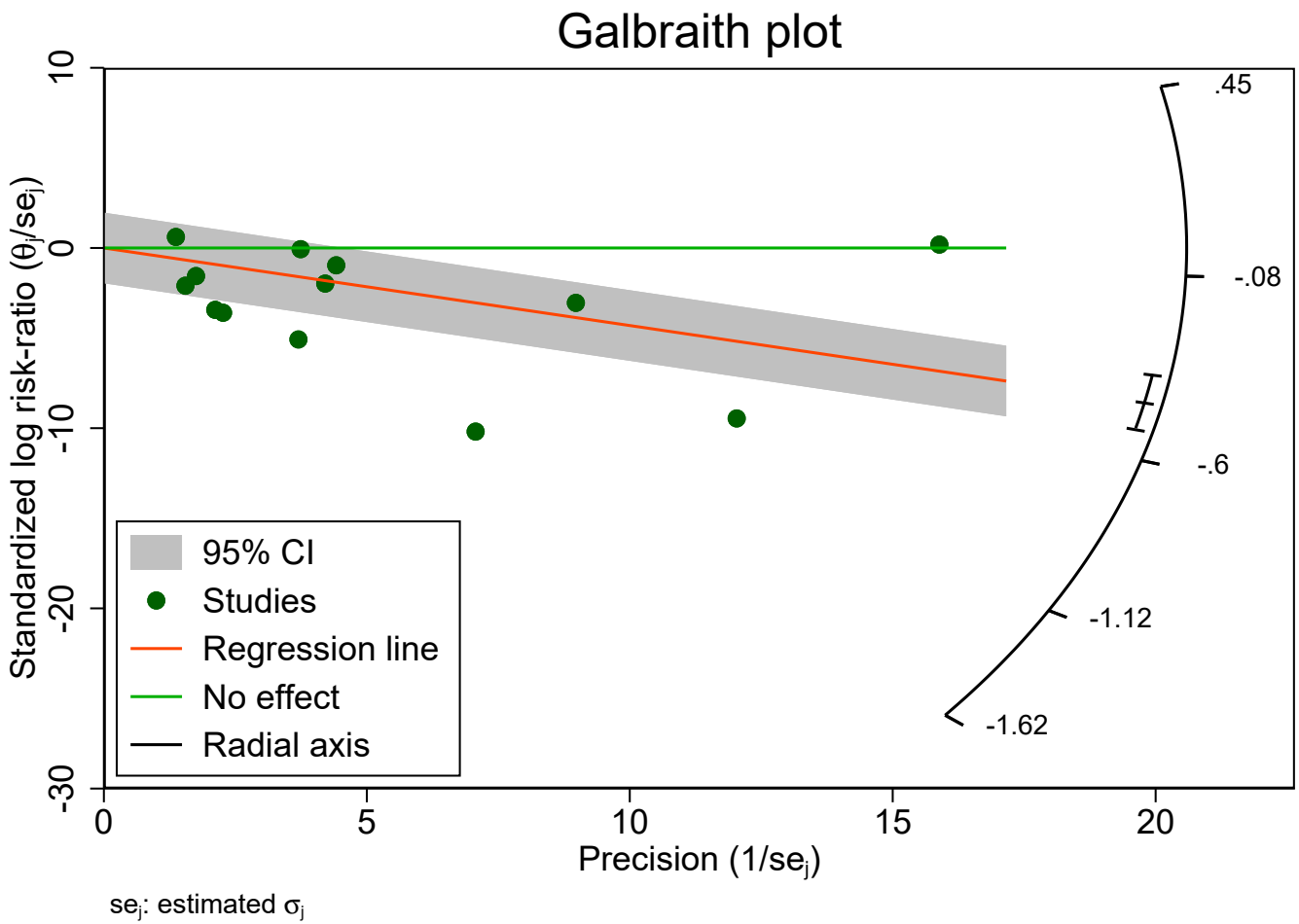
Summary

- Today, we learned how to do the following in Stata:
  - Perform multivariate meta-analysis.
  - Obtain multivariate heterogeneity statistics.
  - Obtain fitted values.
  - Create diagnostic plots.
  - Perform sensitivity analysis.

Multivariate meta-analysis with Stata's graphical interface

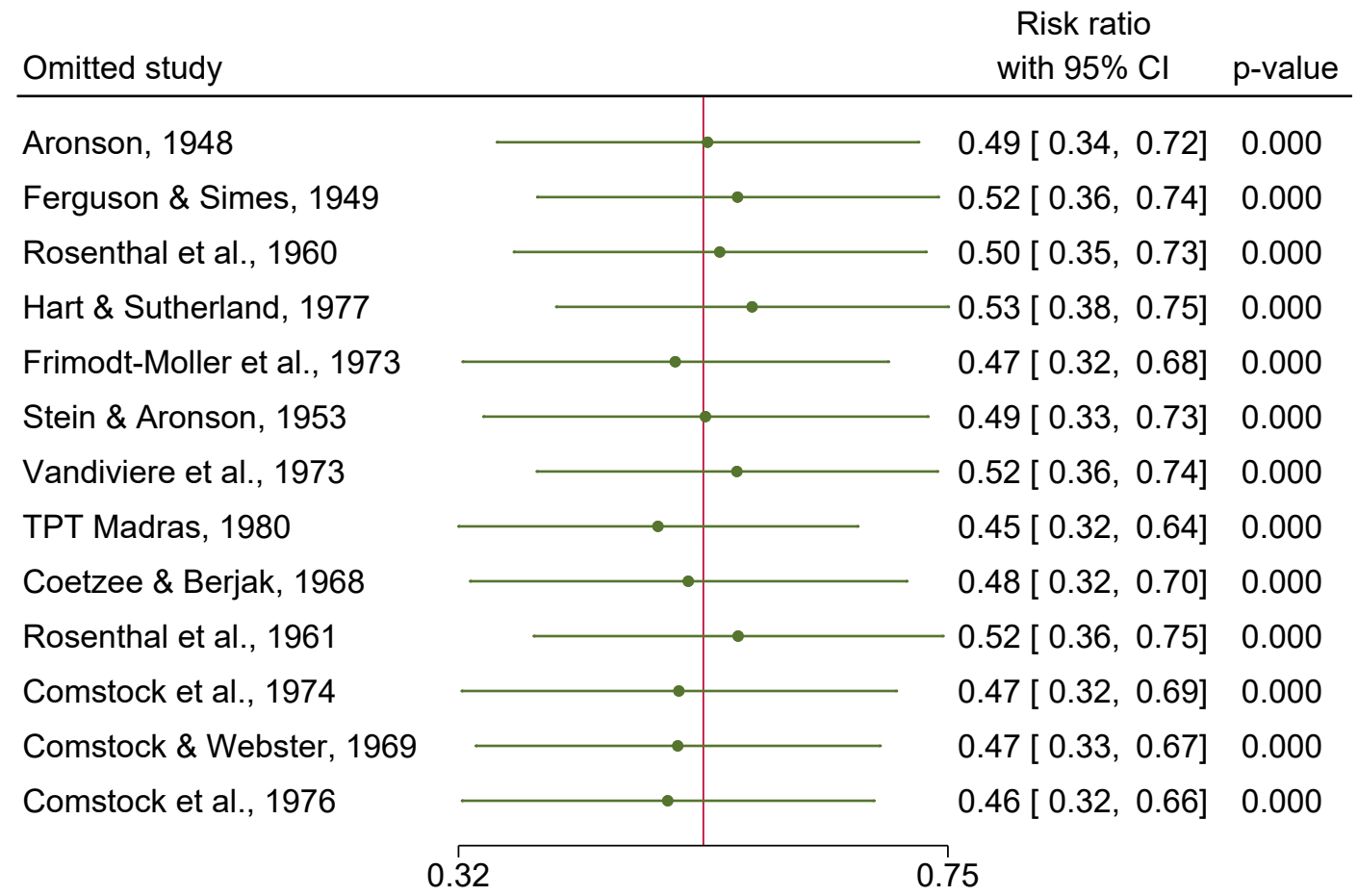


Also new in Stata 17: Galbraith plots



se_j: estimated σ_j

Also new in Stata 17: Leave-one-out meta analysis



Resources

- Overview of Multivariate meta-analysis features in Stata
- *Stata News: Multivariate meta-analysis*
- Video tutorial on performing multivariate meta-analysis in Stata
- *Stata Meta-Analysis Reference Manual*

References

- Antczak-Bouckoms, A., K. Joshipura, E. Burdick, and J. F. Camilla Tulloch. 1993. Meta-analysis of surgical versus non-surgical methods of treatment for periodontal disease. *Journal of Clinical Periodontology* 20: 259–268. https://doi.org/10.1111/j.1600-051X.1993.tb00355.x.
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The end

- Thank you!