Practical 1: Meta-analysis

The aim of this practical is to introduce the **metan** command.

# Diuretics for pre-eclampsia (meta-analysis)

Dataset **diuretics.dta** contains data from nine trials of diuretics for pre-eclampsia (dichotomous outcome). Open the dataset in Stata (either by double clicking the file in Windows to open it in a new Stata session, or by first starting Stata and then opening the file using the menus or the **use** command).

Use the **describe** and **notes** commands to obtain details of the dataset.

We can perform a meta-analysis using the default methods of the **metan** command as follows:

**metan r1 f1 r2 f2**



The default method is a fixed-effect analysis on the risk ratio scale using the Mantel-Haenszel method.

Now type:

**metan r1 f1 r2 f2, or fixedi**



The **or** argument species an analysis on the odds ratio scale and **fixedi** requests a fixed-effect analysis using the standard inverse-variance method.

The random-effects meta-analysis is produced as follows:

**metan r1 f1 r2 f2, or randomi**



The following table lists the options available for methods of meta-analysis of dichotomous outcome data. The option **nograph** suppresses the forest plot, so makes the analysis quicker to run.

|  |  |
| --- | --- |
| **or** | odds ratio |
| **rr** | risk ratio |
| **rd** | risk difference |
| **fixed** | Mantel-Haenszel fixed-effect |
| **random** | Mantel-Haenszel random-effects |
| **fixedi** | Inverse-variance fixed effect |
| **randomi** | Inverse-variance random-effects |

The default method is equivalent to

**metan r1 f1 r2 f2, rr fixed**

Try a few different methods.

Do the methods affect the conclusions you would draw?

|  |
| --- |
| RR fixedi 0.74 (0.64; 0.85)  OR fixedi 0.67 (0.56; 0.79)  RR randomi 0.65 (0.46; 0.90)  OR randomi 0.60 (0.40; 0.89)  RR fixed M-H 0.71 (0.62; 0.82)  RR random M-H 0.65 (0.46; 0.90) |

Use **help metan** to look at the options available for the command. You can make your forest plots look prettier using the following command (for the random-effects meta-analysis):

**metan r1 f1 r2 f2, or randomi label(namevar=study) xlabel(0.1, 0.2, 0.5, 1, 2, 4) effect(Odds ratio) favours(favours diuretic # favours control) texts(180)**

# Meta-analysis for calcium channel blockers versus beta blockers: more about metan (OPTIONAL)

Dataset **diabetes1.dta** contains data from five trials comparing two antihypertensive treatments, calcium channel blockers (CCB) and beta-blockers (BB), measuring the onset of diabetes as an outcome. Use the **describe** and **notes** commands to obtain details of the dataset.

We will start by using the **generate** command to calculate the log odds ratio and its standard error for each study. First, derive the number of individuals who did *not* develop diabetes in the two treatment arms:

**generate f1=n1-r1**

**generate f2=n2-r2**

**list r1 f1 n1 r2 f2 n2**

Note, **r1 f1 n1** are data for BB (treatment 1); **r2 f2 n2** for CCB (treatment 2).

Now derive the odds ratio, then the log odds ratio and its corresponding standard error for each study. We will take the ratio of diabetes odds on CCB over diabetes odds on BB (odds of diabetes for treatment 2 over odds of diabetes for treatment 1).

**gen or=(r2/f2)/(r1/f1)**

**gen logor=log(or)**

**gen selogor=sqrt(1/r2+1/f2+1/r1+1/f1)**

**list study study\_id or logor selogor**

We will now use the **metan** command to perform a fixed- and then a random-effects meta-analysis, using inverse-variance weighting. The basic output for fixed-effects is produced by typing:

**metan logor selogor**

Study | ES [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

1 | -0.104 -0.562 0.353 2.42

2 | -0.384 -0.498 -0.271 39.60

3 | -0.171 -0.288 -0.055 37.36

4 | -0.165 -0.351 0.021 14.60

5 | -0.025 -0.315 0.266 6.02

---------------------+---------------------------------------------------

I-V pooled ES | -0.244 -0.316 -0.173 100.00

---------------------+---------------------------------------------------

Heterogeneity chi-squared = 10.67 (d.f. = 4) p = 0.031

I-squared (variation in ES attributable to heterogeneity) = 62.5%

Test of ES=0 : z= 6.73 p = 0.000



The **metan** command has many options to improve the output. To display the output on the odds ratio scale, and to see the study IDs, type:

**metan logor selogor, eform lcols(study\_id)**

metan logor selogor, eform lcols(study\_id)

Study | ES [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

AASK | 0.901 0.570 1.423 2.42

ASCOT | 0.681 0.608 0.762 39.60

INVEST | 0.842 0.750 0.946 37.36

NORDIL | 0.848 0.704 1.022 14.60

STOP-2 | 0.976 0.730 1.304 6.02

---------------------+---------------------------------------------------

I-V pooled ES | 0.783 0.729 0.841 100.00

---------------------+---------------------------------------------------

Heterogeneity chi-squared = 10.67 (d.f. = 4) p = 0.031

I-squared (variation in ES attributable to heterogeneity) = 62.5%

Test of ES=1 : z= 6.73 p = 0.000

To produce a random-effects analysis:

**metan logor selogor, eform lcols(study\_id) random**

. metan logor selogor, eform lcols(study\_id) random

Study | ES [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

AASK | 0.901 0.570 1.423 7.03

ASCOT | 0.681 0.608 0.762 29.09

INVEST | 0.842 0.750 0.946 28.74

NORDIL | 0.848 0.704 1.022 21.55

STOP-2 | 0.976 0.730 1.304 13.59

---------------------+---------------------------------------------------

D+L pooled ES | 0.813 0.710 0.930 100.00

---------------------+---------------------------------------------------

Heterogeneity chi-squared = 10.67 (d.f. = 4) p = 0.031

I-squared (variation in ES attributable to heterogeneity) = 62.5%

Estimate of between-study variance Tau-squared = 0.0130

Test of ES=1 : z= 3.01 p = 0.003

Complete the following table of results from the random-effects meta-analysis, where we use notation *μ* (logOR) and *τ*2 from the lectures.

Table 1

|  |  |  |
| --- | --- | --- |
| ***Parameter*** | ***Estimate*** | ***95% confidence interval*** |
| *μ* CCB vs BB | -0.207 | -0.342 to -0.072 |
| *ΟR* CCB vs BB | 0.813 | 0.710 to 0.930 |
| *τ*2CCB vs BB | 0.013 | N/A |

The analysis can be performed directly from the binary data as follows:

**metan r2 f2 r1 f1, lcols(study\_id) or randomi**

. metan r2 f2 r1 f1, lcols(study\_id) or randomi nograph

Study | OR [95% Conf. Interval] % Weight

---------------------+---------------------------------------------------

AASK | 0.901 0.570 1.423 7.03

ASCOT | 0.681 0.608 0.762 29.09

INVEST | 0.842 0.750 0.946 28.74

NORDIL | 0.848 0.704 1.022 21.55

STOP-2 | 0.976 0.730 1.304 13.59

---------------------+---------------------------------------------------

D+L pooled OR | 0.813 0.710 0.930 100.00

---------------------+---------------------------------------------------

Heterogeneity chi-squared = 10.67 (d.f. = 4) p = 0.031

I-squared (variation in OR attributable to heterogeneity) = 62.5%

Estimate of between-study variance Tau-squared = 0.0130

Test of OR=1 : z= 3.01 p = 0.003

The **or** option specifies use of odds ratios (alternatives are **rr** and **rd** for risk ratios and risk differences, respectively), and the **randomi** option specifies a random-effects analysis using a standard inverse-variance weighted average. To suppress the forest plot, add the option **nograph**.

Check that the results agree with the analysis above.

The **metan** command stores the estimated treatment effects and the standard errors of the log effect for each study in the automatically created variables **\_ES** (effect size) and **\_selogES**. For example, if we use the **metan** command with odds ratios then **\_ES** is the odds ratio (identical to the variable or calculated at the beginning of the practical) and the value of **\_selogES** is the standard error of the log odds ratio (identical to variable **selogor**, also calculated earlier).

. list study or \_ES selogor \_selogES

+---------------------------------------------------+

| study or \_ES selogor \_selogES |

|---------------------------------------------------|

1. | 1 .9008403 .9008403 .2332448 .2332448 |

2. | 5 .680837 .680837 .0576991 .0576991 |

3. | 14 .8424562 .8424562 .0594049 .0594049 |

4. | 16 .8480348 .8480348 .0950086 .0950086 |

5. | 22 .9757153 .9757153 .1480106 .1480106 |

+---------------------------------------------------+

*Note:* Some Stata meta-analysis commands require the user to provide the log odds ratio and its standard error; the **metan** command is useful for deriving these variables, as it is quicker than computing them directly.

**metan r2 f2 r1 f1, lcols(study\_id) or randomi nograph**

**list study or \_ES selogor \_selogES**

In addition, **metan** stores the results of the meta-analysis. We can see these using

**return list**

Use the following commands to complete the following table (**g** is shorthand for **generate**):

**g mu = log(r(ES))**

**display mu**

**display r(selogES)**

**display r(ES)**

**display r(ci\_low)**

**display r(ci\_upp)**

**display r(tau2)**

. display mu

-.207302

. display r(selogES)

.0688336

. display r(ES)

.81277415

. display r(ci\_low)

.71019665

. display r(ci\_upp)

.93016746

. display r(tau2)

.01295884

Table 2

|  |  |  |
| --- | --- | --- |
| ***Parameter*** | ***Estimate*** | ***Uncertainty*** |
| *μ* CCB vs BB | -0.207 | Standard error: 0.0688 |
| *ΟR* CCB vs BB | 0.813 | 95% Confidence interval:  0.710 to 0.930 |
| *τ*2CCB vs BB | 0.130 | N/A |

*Note:* An alternative way to obtain results on the log odds ratio scale is to use the option **log** in the **metan** command.

Practical 2: Fitting the network meta-analysis model

In this practical we will perform network meta-analysis with multivariate meta-analysis (with **network**).

# Network meta-analysis using multivariate meta-analysis

We will use the **network** package that calls the **mvmeta** command, so that we can properly take account of the multi-arm studies. The package does everything ‘automatically’, but make sure you understand each step so that you know what is going on.

We will use a different data set that has been formatted more appropriately for **network**. Open **diabetes2.dta**.

The treatments codes are:

1 = placebo, 2 = beta blockers (BB), 3 = diuretics, 4 = calcium channel blockers (CCB), 5 = ACE inhibitors, 6 = angiotensin-receptor blockers (ARB).

Look at part of the data, e.g.

**list study t r n**

+------------------------+

| study t r n |

|------------------------|

1. | 1 5 45 410 |

2. | 1 2 70 405 |

3. | 1 4 32 202 |

4. | 2 5 119 4096 |

5. | 2 4 154 3954 |

|------------------------|

6. | 2 3 302 6766 |

7. | 3 6 1 196 |

8. | 3 3 8 196 |

9. | 4 5 138 2800 |

10. | 4 3 200 2826 |

|------------------------|

11. | 5 2 799 7040 |

12. | 5 4 567 7072 |

13. | 6 5 337 5183 |

14. | 6 2 380 5230 |

15. | 7 6 163 2715 |

|------------------------|

16. | 7 1 202 2721 |

17. | 8 5 449 2623 |

18. | 8 1 489 2646 |

19. | 9 3 29 416 |

20. | 9 1 20 424 |

|------------------------|

21. | 10 4 177 4841 |

22. | 10 1 154 4870 |

23. | 11 2 86 3297 |

24. | 11 3 75 3272 |

25. | 12 5 102 2837 |

|------------------------|

26. | 12 1 155 2883 |

27. | 13 4 136 2508 |

28. | 13 3 176 2511 |

29. | 14 2 665 8078 |

30. | 14 4 569 8098 |

|------------------------|

31. | 15 6 242 4020 |

32. | 15 2 320 3979 |

33. | 16 2 37 1102 |

34. | 16 3 43 1081 |

35. | 16 1 34 2213 |

|------------------------|

36. | 17 2 251 5059 |

37. | 17 4 216 5095 |

38. | 18 5 335 3432 |

39. | 18 1 399 3472 |

40. | 19 6 93 2167 |

|------------------------|

41. | 19 1 115 2175 |

42. | 20 3 140 1631 |

43. | 20 1 118 1578 |

44. | 21 5 93 1970 |

45. | 21 2 97 1960 |

|------------------------|

46. | 21 4 95 1965 |

47. | 22 6 690 5087 |

48. | 22 4 845 5074 |

+------------------------+

What does each row in the data set represent?

|  |
| --- |
| A study arm. |

We now need to create the treatment effect estimates and a variance-covariance matrix for the observations. Recall that the multivariate approach requires us to have data for the reference treatment in every study (lecture 7).

**network setup r n, stud(study) trt(t) ref(1) or numcodes**

Look again at the data

**edit**

How many rows are there per study?

|  |
| --- |
| One. |

What does each variable **\_y\_2**, **\_y\_3**,**…**, **\_y\_6** represent?

|  |
| --- |
| The log odds ratio for each comparison against placebo. |

What does each variable **\_S\_2\_2**, **\_S\_3\_3**,**…**, **\_S\_6\_6** represent?

|  |
| --- |
| The variance of the log odds ratios for each comparison against placebo. |

What does each variable **\_S\_2\_3**, **\_S\_2\_4**,**…**, **\_S\_5\_6** represent?

|  |
| --- |
| The covariance for each pair of comparisons against placebo (which is computed as the variance of the log odds of diabetes in the placebo group). |

Network command allows you to switch between the format of the data:

**network convert pairs**

Look again at the data. How many rows are there per study? Use the sort command if needed (**sort study**)

|  |
| --- |
| 1 row for 2-armed studies, 3 rows for three-armed studies |

There is also a third form:

**network convert standard**

Now use the map option to get a network graph:

**network map**

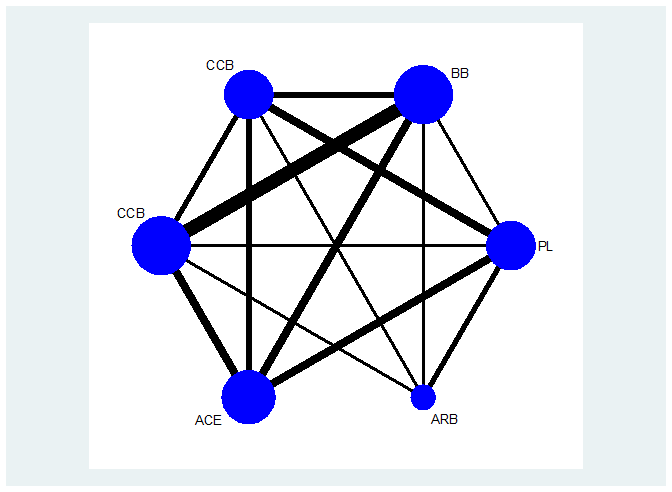
The graph can be exported from Stata in other programs for editing (eg. PowerPoint)

By typing help network you can also explore additional options for this command.

If you bring the data in the pairs format, you can also use the networkplot command, which allows some additional options

**network convert pairs**

**networkplot \_t1 \_t2, lab(PL BB CCB CCB ACE ARB)**

****

To run the network meta-analysis:

**network convert augmented**

**network meta c**

network convert augmented

Converting pairs to augmented ...

. network meta c

Command is: mvmeta \_y \_S, bscov(prop 0.5\*I(5)+J(5,5,0.5)) longparm

Note: using method reml

Note: using variables \_y\_2 \_y\_3 \_y\_4 \_y\_5 \_y\_6

Note: 22 observations on 5 variables

Warning: method of moments failed - I2 statistic not available

Note: variance-covariance matrix is proportional to 0.5\*I(5)+J(5,5,0.5)

initial: log likelihood = -99.552094

rescale: log likelihood = -84.191458

rescale eq: log likelihood = -77.866909

Iteration 0: log likelihood = -77.866909

Iteration 1: log likelihood = -76.863754

Iteration 2: log likelihood = -76.499235 (not concave)

Iteration 3: log likelihood = -76.175552 (not concave)

Iteration 4: log likelihood = -76.165143

Iteration 5: log likelihood = -76.154398

Iteration 6: log likelihood = -76.154249

Iteration 7: log likelihood = -76.154249

Multivariate meta-analysis

Variance-covariance matrix = proportional 0.5\*I(5)+J(5,5,0.5)

Method = reml Number of dimensions = 5

Restricted log likelihood = -76.154249 Number of observations = 22

------------------------------------------------------------------------------

| Coef. Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

\_y\_2 |

\_cons | .2121632 .0810328 2.62 0.009 .0533419 .3709845

-------------+----------------------------------------------------------------

\_y\_3 |

\_cons | .2806863 .0842851 3.33 0.001 .1154905 .4458822

-------------+----------------------------------------------------------------

\_y\_4 |

\_cons | .0404374 .0786068 0.51 0.607 -.1136291 .1945038

-------------+----------------------------------------------------------------

\_y\_5 |

\_cons | -.1233222 .0679924 -1.81 0.070 -.2565848 .0099405

-------------+----------------------------------------------------------------

\_y\_6 |

\_cons | -.1910824 .0874815 -2.18 0.029 -.3625429 -.0196219

------------------------------------------------------------------------------

Estimated between-studies SDs and correlation matrix:

SD \_y\_2 \_y\_3 \_y\_4 \_y\_5 \_y\_6

\_y\_2 .11682054 1 . . . .

\_y\_3 .11682054 .5 1 . . .

\_y\_4 .11682054 .5 .5 1 . .

\_y\_5 .11682054 .5 .5 .5 1 .

\_y\_6 .11682054 .5 .5 .5 .5 1

By default, the command uses the common assumption of equal heterogeneities for all comparisons. That is, we assumed a variance-covariance matrix of the following form for the five basic parameters.



Which treatments would appear to be best, and worst (versus placebo)? Note that r in the data are incidence of diabetes and that the *Coef*. reported in STATA is the logOR of each treatment versus placebo.

|  |
| --- |
| Treatment 6 (ARB) appears to be associated with the lowest incidence of diabetes, and treatment 3 (diuretics) with the highest. |

Compute (‘by hand’) the odds ratio comparing ACE (treatment 5) with BB (treatment 2).

|  |
| --- |
| This can be obtained most directly as the ratio of odds ratios for ACEvsPLAC (**\_y\_5**) compared with BBvsPLAC (**\_y\_2**):  ORACEvsBB = 0.8840 / 1.2363 = 0.715 |

We can use the **lincom** command to compare specific treatments. To compare ACE (treatment 5) with BB (treatment 2):

. lincom [\_y\_5]\_cons -[ \_y\_2]\_cons, eform

( 1) - [\_y\_2]\_cons + [\_y\_5]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .7149908 .0526174 -4.56 0.000 .618955 .8259275

------------------------------------------------------------------------------

The variance-covariance matrix of the coefficients:

. mat li e(V)

symmetric e(V)[6,6]

\_y\_B: \_y\_C: \_y\_D: \_y\_E: \_y\_F: tau:

\_cons \_cons \_cons \_cons \_cons \_cons

\_y\_B:\_cons .00656634

\_y\_C:\_cons .00343416 .00710403

\_y\_D:\_cons .00459836 .00354729 .00617906

\_y\_E:\_cons .00288678 .00264034 .00260626 .00462297

\_y\_F:\_cons .00326622 .00207963 .00326302 .00165306 .00765301

tau:\_cons .00050579 .00065701 .00067637 .000105 .00019906 .00153453

To derive all summary odds ratios for all treatment comparisons based on the consistency equations, run the following loop.

. foreach trt1 in 2 3 4 5 6{

2. foreach trt2 in 2 3 4 5 6{

3. if "`trt1'"=="`trt2'" continue

4. if "`trt2'">"`trt1'" lincom [\_y\_`trt2']\_cons-[\_y\_`trt1']\_cons,eform

5. }

6. }

( 1) - [\_y\_2]\_cons + [\_y\_3]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | 1.070926 .0883241 0.83 0.406 .911081 1.258815

------------------------------------------------------------------------------

( 1) - [\_y\_2]\_cons + [\_y\_4]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .8422101 .0501711 -2.88 0.004 .7494 .9465143

------------------------------------------------------------------------------

( 1) - [\_y\_2]\_cons + [\_y\_5]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .7149912 .0526175 -4.56 0.000 .6189552 .8259279

------------------------------------------------------------------------------

( 1) - [\_y\_2]\_cons + [\_y\_6]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .668148 .0585798 -4.60 0.000 .5626569 .7934174

------------------------------------------------------------------------------

( 1) - [\_y\_3]\_cons + [\_y\_4]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .7864317 .0618662 -3.05 0.002 .6740616 .9175347

------------------------------------------------------------------------------

( 1) - [\_y\_3]\_cons + [\_y\_5]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .6676384 .0536041 -5.03 0.000 .5704257 .7814181

------------------------------------------------------------------------------

( 1) - [\_y\_3]\_cons + [\_y\_6]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .6238975 .0642274 -4.58 0.000 .509901 .7633798

------------------------------------------------------------------------------

( 1) - [\_y\_4]\_cons + [\_y\_5]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .8489464 .0634699 -2.19 0.028 .7332325 .9829214

------------------------------------------------------------------------------

( 1) - [\_y\_4]\_cons + [\_y\_6]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .793327 .0678099 -2.71 0.007 .6709582 .9380133

------------------------------------------------------------------------------

( 1) - [\_y\_5]\_cons + [\_y\_6]\_cons = 0

------------------------------------------------------------------------------

| exp(b) Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

(1) | .9344842 .0885043 -0.72 0.474 .7761673 1.125094

------------------------------------------------------------------------------

You can create a table of all results in the network by running the netleague command .The table is stored at the right end of the dataset

. netleague,eform

Warning: The existing dataset is stored as a temporary file

Warning: To save any changes applied at this temporary file in a specific directory you need to us

> e the 'Save as' menu

The league table has been stored at the end of the dataset

You can obtain a ranking of the treatments by running

. network rank min, mean

Command is: mvmeta, noest pbest(min in 1, zero id(study) mean stripprefix(\_y\_) zeroname(1) rename(

> 1 = 1, 2 = 2, 3 = 3, 4 = 4, 5 = 5, 6 = 6))

Estimated probabilities (%) of each treatment being the best (and other ranks)

- assuming the minimum parameter is the best

- using 1000 draws

- allowing for parameter uncertainty

----------------------------------------------

study and | Treatment

Rank | 1 2 3 4 5 6

----------+-----------------------------------

1 |

Best | 0.1 0.0 0.0 0.0 24.9 75.0

2nd | 4.7 0.0 0.0 2.4 69.3 23.6

3rd | 64.5 0.0 0.0 28.6 5.7 1.2

4th | 30.5 0.4 0.4 68.4 0.1 0.2

5th | 0.2 80.0 19.2 0.6 0.0 0.0

Worst | 0.0 19.6 80.4 0.0 0.0 0.0

MEAN RANK | 3.3 5.2 5.8 3.7 1.8 1.3

SUCRA | 0.5 0.2 0.0 0.5 0.8 0.9

----------------------------------------------

mvmeta command is stored in F9

As a reminder:

**1 = placebo, 2 = beta blockers (BB), 3 = diuretics, 4 = calcium channel blockers (CCB), 5 = ACE inhibitors, 6 = angiotensin-receptor blockers (ARB).**

Extract these results:

Table 2

|  |  |  |
| --- | --- | --- |
| ***Parameter*** | ***Estimate*** | ***Uncertainty*** |
| ORCCB vs BB | 0.842 | CI: 0.749 to 0.947 |
| ORACE vs BB | 0.715 | CI: 0.619 to 0.826 |
| ORACE vs CCB | 0.849 | CI: 0.733 to 0.983 |
| *τ*2 | 0.11682 = 0.014 | - |

In this analysis we chose treatment 1 to be the reference. As discussed in the lectures, this choice is arbitrary. Check that redoing the analyses using another treatment does not substantially change results. There might be some small differences due to augmentation technique. In general, for estimation purposes it is good to choose well connected treatments.

# Forest plot of all pairwise summary effects

We can use the **intervalplot** command to draw a forest plot of all estimated pairwise summary effects. The option **null()** specifies the line of no effect, while the option **separate** separates the different comparisons according to the comparator treatment. The options **range()**  and **xlab()** handle the appearance of the horizontal axis and the option **margin()** the blank margins around the plot:

**intervalplot, mvmeta lab(Placebo BB Diuretics CCB ACE ARB) eform**

**null(1) sep range(0.4 2) xlab(0.4 0.7 1.5 2) marg(5 40 5 5)**



We can further use the predictive intervals to show how the different comparisons are affected by the estimation of the (common) heterogeneity with respect to the additional uncertainty anticipated in future studies.

# Example with continuous data (OPTIONAL)

Open the data set **glaucoma.dta**. There are 24 studies and eight treatments. The treatment codes are:

**1 = placebo**, **2 = travoprost**, **3 = timolol**, **4 = betaxolol**, **5 = latanoprost**, **6 = dorzolamide**, **7 = brinzolamide**, **8 = brimonidine**, **9 = bimatoprost**.

**use "glaucoma.dta", clear**

Look at part of the data, e.g.

**list study t mean sd n**

Prepare the data in the appropriate format for conducting network meta-analysis using the multivariate approach (consider the treatment 1 as reference).

**network setup mean sd n,stud(study) trt(t) smd ref(1) numcodes**

Look again at the data

**edit**

How many rows are there per study?

|  |
| --- |
| One |

What does each variable **\_y\_2**, **\_y\_3**,**…**, **\_y\_6** represent?

|  |
| --- |
| The SMD for each treatment against placebo. |

What does each variable **\_S\_2\_2**, **\_S\_3\_3**,**…**, **\_S\_6\_6** represent?

|  |
| --- |
| The variance of the SMD for each comparison against placebo. |

What does each variable **\_S\_2\_3**, **\_S\_2\_4**,**…**, **\_S\_5\_6** represent?

|  |
| --- |
| The covariance for each pair of comparisons against placebo (covariance of the comparison 2vs1 and 3vs1). |

Network command allows you to switch between the format of the data:

**network convert pairs**

Look again at the data. How many rows are there per study? Use the sort command if needed (**sort study**)

|  |
| --- |
| 1 row for 2-armed studies, 3 rows for three-armed studies |

Now use the map option to get a network graph:

**network map**



To run the network meta-analysis:

**network convert augmented**

**network meta c**

By default, the command uses the common assumption of equal heterogeneities for all comparisons. That is, we assumed a variance-covariance matrix of the following form for the five basic parameters.



Which treatments would appear to be best, and worst (versus placebo)?

|  |
| --- |
| Y\_9 the best and y\_4 the worst |

Compute (‘by hand’) the SMD comparing treatment 3 with treatment 2.

|  |
| --- |
| This can be obtained most directly as the difference of **\_y\_3** and **\_y\_2**):  SMD3vs2 = -0.436+0.489=0.053 |

To derive all summary SMD for all treatment comparisons based on the consistency equations, run the following loop.

**foreach trt1 in 2 3 4 5 6 7 8 9 {**

**foreach trt2 in 2 3 4 5 6 7 8 9 {**

**if "`trt1'"=="`trt2'" continue**

**if "`trt2'">"`trt1'" lincom [\_y\_`trt2']\_cons-[\_y\_`trt1']\_cons,eform**

**}**

**}**

Extract these results:

Table 2

|  |  |  |
| --- | --- | --- |
| ***Parameter*** | ***Estimate*** | ***Uncertainty*** |
| OR3 vs 2 | .0535011 | CI: -.1133916;.2203939 |
| OR4 vs 2 | 1.232339 | CI: .8537376 1.610939 |
| OR4 vs 3 | 1.178837 | CI: .8304909 1.527184 |
| *τ*2 | .1392655^2 | - |

Practical 3: Assessing inconsistency in network meta-analysis

# Loop-specific approach for the evaluation of inconsistency

Open the data set **diabetes2.dta**.

The treatment codes are:

**1 = placebo**, **2 = beta blockers (BB)**, **3 = diuretics**, **4 = calcium channel blockers (CCB)**, **5 = ACE inhibitors, 6 = angiotensin-receptor blockers (ARB)**.

Use the **network** package to prepare the data in a format where each row represents a pairwise comparison from a study

**network setup r n, stud(study) trt(t) ref(1) or**

**network convert pairs**

Use the **ifplot** command to draw a forest plot of all inconsistency factors. The option **eform** plots the ratio of odds ratios (*ROR*) between direct and indirect estimates, which is estimated as *ROR=exp(IF)*. We can use the option **plotoptions()**to handle the appearance of the plot using standard options of the **metan** command:

**ifplot \_y \_stderr \_t1 \_t2 study, eform lab(P BB D CCB ACE ARB) plotopt(texts(120))**

16 triangular loops found

Note: Heterogeneity of loop P-BB-D cannot be estimated due to insufficient observations - set equal to 0

Note: Heterogeneity of loop P-BB-ARB cannot be estimated due to insufficient observations - set equal to 0

Note: Heterogeneity of loop P-CCB-ARB cannot be estimated due to insufficient observations - set equal to 0

Note: Heterogeneity of loop BB-D-ARB cannot be estimated due to insufficient observations - set equal to 0

Note: Heterogeneity of loop D-CCB-ARB cannot be estimated due to insufficient observations - set equal to 0

Evaluation of inconsistency using loop-specific heterogeneity estimates:

+---------------------------------------------------------------------------+

| Loop | ROR | z\_value | p\_value | CI\_95 | Loop\_Heterog\_tau2 |

|------------+-------+---------+---------+--------------+-------------------|

| BB-D-ARB | 6.269 | 1.704 | 0.088 | (1.00,51.78) | 0.000 |

| D-CCB-ARB | 5.347 | 1.567 | 0.117 | (1.00,43.52) | 0.000 |

| P-D-ARB | 4.154 | 1.168 | 0.243 | (1.00,45.29) | 0.063 |

| P-BB-ACE | 2.295 | 2.478 | 0.013 | (1.19,4.43) | 0.014 |

| P-BB-ARB | 2.041 | 2.638 | 0.008 | (1.20,3.47) | 0.000 |

| P-BB-D | 1.781 | 1.932 | 0.053 | (1.00,3.20) | 0.000 |

| P-BB-CCB | 1.557 | 1.393 | 0.164 | (1.00,2.90) | 0.013 |

| BB-CCB-ACE | 1.342 | 1.645 | 0.100 | (1.00,1.90) | 0.014 |

| BB-D-ACE | 1.318 | 1.347 | 0.178 | (1.00,1.97) | 0.006 |

| P-D-ACE | 1.260 | 0.841 | 0.400 | (1.00,2.16) | 0.026 |

| BB-CCB-ARB | 1.147 | 0.675 | 0.500 | (1.00,1.71) | 0.013 |

| P-CCB-ARB | 1.142 | 0.874 | 0.382 | (1.00,1.54) | 0.000 |

| P-CCB-ACE | 1.140 | 0.606 | 0.544 | (1.00,1.74) | 0.011 |

| P-D-CCB | 1.115 | 0.259 | 0.795 | (1.00,2.55) | 0.058 |

| D-CCB-ACE | 1.092 | 0.520 | 0.603 | (1.00,1.52) | 0.000 |

| BB-D-CCB | 1.012 | 0.059 | 0.953 | (1.00,1.49) | 0.011 |

+---------------------------------------------------------------------------+

****

ROR stands for the ratio of odds ratios between direct and indirect evidence.

How many closed loops are included in the network?

|  |
| --- |
| 16 |

How many loops display significant inconsistency in the network?

|  |
| --- |
| 2 (P-BB-ACE and P-BB-ARB) |

Are there other loops that might be potential sources of inconsistency in the network?

|  |
| --- |
| For example loops with ROR>2 (BB-D-ARB, D-CCB-ARB, P-D-ARB) |

The default setting for **ifplot** is to assume a common heterogeneity variance for all comparisons in a loop. Run the command again allowing this to differ for each comparison in a loop (comparison-specific heterogeneity estimates):

**ifplot \_y \_stderr \_t1 \_t2 study, eform lab(P BB D CCB ACE ARB) tau2(comparison)**

+-------------------------------------------------------+

| Loop | ROR | z\_value | p\_value | CI\_95 |

|------------+-------+---------+---------+--------------|

| BB-D-ARB | 6.209 | 1.692 | 0.091 | (1.00,51.50) |

| D-CCB-ARB | 5.347 | 1.567 | 0.117 | (1.00,43.52) |

| P-D-ARB | 4.042 | 1.266 | 0.206 | (1.00,35.14) |

| P-BB-ACE | 2.275 | 2.970 | 0.003 | (1.32,3.91) |

| P-BB-ARB | 2.041 | 2.638 | 0.008 | (1.20,3.47) |

| P-BB-D | 1.799 | 1.914 | 0.056 | (1.00,3.28) |

| P-BB-CCB | 1.557 | 1.616 | 0.106 | (1.00,2.66) |

| BB-CCB-ACE | 1.334 | 1.643 | 0.100 | (1.00,1.88) |

| P-D-ACE | 1.324 | 0.951 | 0.341 | (1.00,2.36) |

| BB-D-ACE | 1.293 | 1.277 | 0.201 | (1.00,1.92) |

| P-D-CCB | 1.158 | 0.481 | 0.630 | (1.00,2.10) |

| BB-CCB-ARB | 1.147 | 1.100 | 0.271 | (1.00,1.47) |

| P-CCB-ARB | 1.142 | 0.874 | 0.382 | (1.00,1.54) |

| P-CCB-ACE | 1.141 | 0.742 | 0.458 | (1.00,1.61) |

| D-CCB-ACE | 1.045 | 0.199 | 0.843 | (1.00,1.61) |

| BB-D-CCB | 1.012 | 0.066 | 0.947 | (1.00,1.44) |

+-------------------------------------------------------+

****

Do the results change?

|  |
| --- |
| no |

Run the command using the common between-study variance estimated by the network meta-analysis model for all loops from the previous practical (i.e. set τ2 = 0.116820212):

**di .1168^2**

**ifplot \_y \_stderr \_t1 \_t2 study, eform lab(P BB D CCB ACE ARB) tau2(0.014)**

Do the results change?

|  |
| --- |
| no |

# Assessing inconsistency using the node-splitting approach

We can assess inconsistency using the node-splitting approach. In order to split comparison A-B type:

**network sidesplit A B**

network sidesplit A B

------------------------------------------------------------------------------

| Coef. Std. Err. z P>|z| [95% Conf. Interval]

-------------+----------------------------------------------------------------

direct | .7922931 .2628797 3.01 0.003 .2770583 1.307528

indirect | .1551618 .0796555 1.95 0.051 -.0009602 .3112838

difference | .6371313 .2746841 2.32 0.020 .0987605 1.175502

------------------------------------------------------------------------------

Is there a difference between direct and indirect evidence for this comparison?

|  |
| --- |
| There is strong evidence (p-value=0.02) |

You can use network to perform node-splitting to all comparisons in one go:

**network sidesplit all**

network sidesplit all

Side Direct Indirect Difference

Coef. Std. Err. Coef. Std. Err. Coef. Std. Err. P>|z|

A B .7922931 .2628797 .1551618 .0796555 .6371313 .2746841 0.020

A C .4080382 .1360602 .2009533 .1078467 .2070849 .173562 0.233

A D .1502847 .1612496 .0081507 .0898016 .142134 .1845691 0.441

A E -.2041114 .0847437 .0144004 .1102988 -.2185119 .1395455 0.117

A F -.2238881 .1246259 -.1524683 .1323724 -.0714198 .1817941 0.694

B C -.0082547 .1583071 .0987661 .0988051 -.1070208 .186363 0.566

B D -.2134329 .0662229 -.0672686 .1077596 -.1461642 .1288634 0.257

B E -.1615765 .0861535 -.4971921 .0878459 .3356156 .122148 0.006

B F -.3113882 .1510111 -.4557569 .1129874 .1443687 .1886014 0.444

C D -.2066408 .1157759 -.2717753 .1122716 .0651344 .1615246 0.687

C E -.40845 .1175773 -.4043537 .1157525 -.0040963 .1649587 0.980

C F -2.115994 1.071885 -.4565585 .1026226 -1.659436 1.076787 0.123

D E -.2250558 .1153067 -.1218268 .0974226 -.1032291 .1509517 0.494

D F -.241602 .1378063 -.2292368 .1191281 -.0123652 .1821594 0.946

How many treatment comparisons have some indication for inconsistency?

|  |
| --- |
| (AvsB and BvsE) |

How do results compare with the loop-specific approach?

|  |
| --- |
| These two comparisons were also present in the loops identified as suspicious using the loop-specific approach |