

Practical: Network Meta-Analysis using MetaInsight worksheet

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This practical uses the newly developed CRSU app *MetaInsight (Continuous)* which can be accessed from <https://crsu.shinyapps.io/metainsightc/>

We have also developed MetaInsight (Binary) for binary data:

<https://crsu.shinyapps.io/metainsightb/>

MetaInsight is a web-based App for conducting network meta-analysis for binary and continuous outcomes using fixed or random effects models. It may also be used to facilitate sensitivity analysis via the inclusion and exclusion of studies as this practical will demonstrate.

After completing this practical, you will be able to....

- Upload data into *MetaInsight*
- Perform a network meta-analysis in *MetaInsight* and interpret the results
- Examine the influence on the results when studies are included and excluded in a sensitivity analysis

In this practical you will be using a real network meta-analysis dataset comparing drug treatments and placebo for reducing obesity (Gray LJ, et al. *A systematic review and mixed treatment comparison of pharmacological interventions for the treatment of obesity. Obes Rev. 2012 Jun;13(6):483-98.*). Interest lies in which of the interventions is most effective for reducing weight. The outcome measure in each study arm is weight loss from study baseline in kilograms. (The whole dataset comes ready loaded into the App but you are going to start by only looking at a subset of the data and learning to load the data into the App).

Firstly, open the *MetaInsight* App in a web browser on your computer:

<https://crsu.shinyapps.io/metainsightc/>

The outcome for the analysis is continuous so we will use the “MetaInsight (continuous)” app.

To load the data into the app, please click ‘Load Data’ page. MetaInsight v1.1 allows data in both long format (1 study arm per row) and wide format (1 whole study per row). On the left hand sidebar of this page, you will see ‘Step 1’ which contains an upload bar for uploading the data and ‘Step 2’ which contains a box for uploading the treatment labels. Instructions on how to upload data and labels are on the main panel (right side) of this page. ‘Long format upload’ tab contains instructions for uploading long format data and similarly, ‘Wide format upload’ tab for uploading wide format data. ‘Data for Analysis’ tab will display any data that are uploaded. Please note that these will have data in already as the App comes with an example dataset already included for illustration purposes.

The long format data should contain six columns with the following exact headings (case sensitive): ‘StudyID’, ‘Study’ (study name), ‘T’(treatment code), ‘N’(number of participants for each arm), ‘Mean’(the mean value of the outcome in each arm, i.e. in this example it would be change in weight from baseline), and ‘SD’ (the Standard deviation of the outcome in each arm). **Please note that the reference treatment needs to be labelled as 1.**

The second box includes the labels for each of the treatment codes. The first row must be 'Number' tabspace 'Label' as shown in the pre-loaded format, case sensitive.

The pre-loaded example data, and the treatment labels, presented in the correct format, can be downloaded by clicking the 'Download' button on the page.

If you prefer the wide format data, similar to the long format instruction tab, you could find the detailed instructions on the 'Wide format upload' tab. The example data in wide format could also be downloaded. Please note that, if you used a previous version of MetaInsight, the treatment labels no longer need to be entered in a descending order, i.e. they can be entered in any order.

PART ONE:

Initially we are going to keep things simple by including only comparisons between three treatments: Orlistat, Sibutramine and Placebo.

The data file, named 'Data_3treatments.csv', and the treatment label file, named 'labels_3treatments.txt' can both be downloaded from

<http://www.nihrcrsu.org/workshops/cochranesymposium2019/>

- i) Step 1: Load the data by selecting the downloaded data file in your local drive.
- ii) Step 2: Load the treatment labels from the downloaded 'labels_3treatments' file by copying and pasting it into the box under 'Step 2' on the side bar.
- iii) Check if the data are uploaded correctly in the 'Data for Analysis' tab and answer the following question:

Question: Most studies only have 2-arms, but three studies have 3-arms. Which are the 3-arm studies?

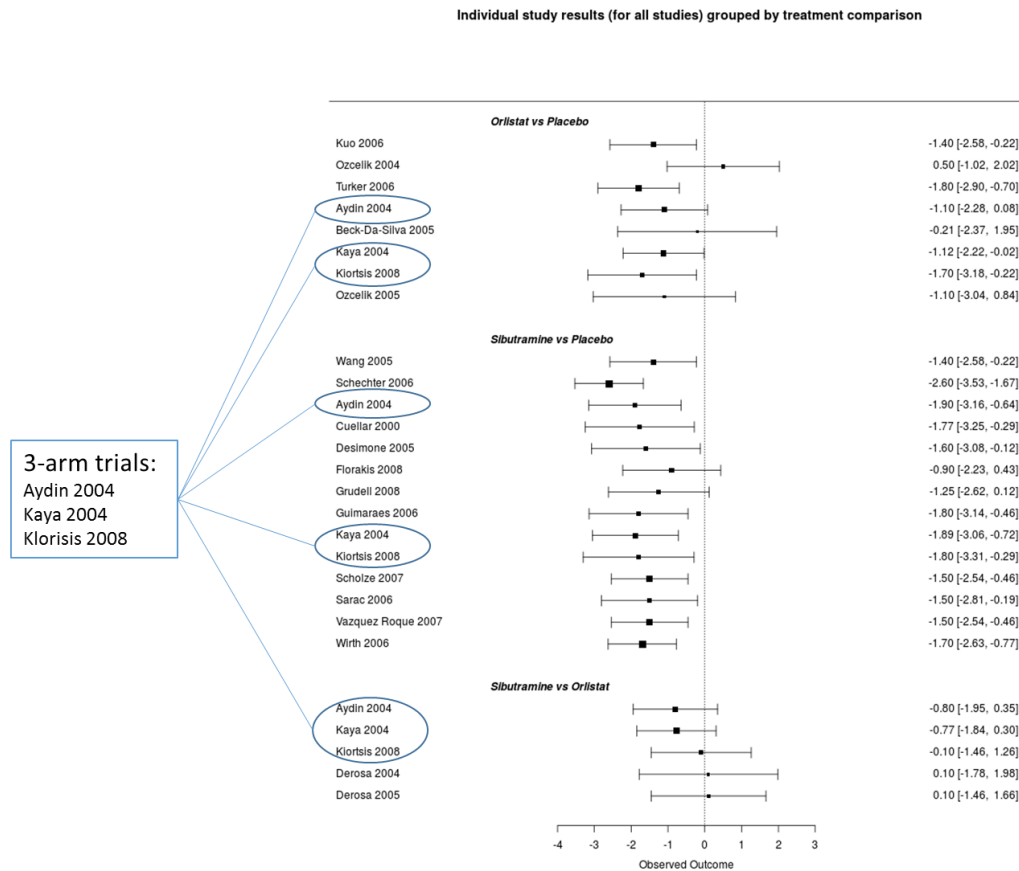
Answer:

Aydin 2004, Kaya 2004, Kiortsis 2008

- iv) Click on 'Data analysis' at the top of the page and you will see two tabs under this page:
 1. Data summary, which contains:
 - 1a. Study Results, and
 - 1b. Network Plot, and
 2. Frequentist network meta-analysis, which contains:
 - 2a. Forest plot, and
 - 2b. Comparison of all treatment pairs, and
 - 2c. Inconsistency

Next, we will explain what these tabs are for.

- v) '1a. Study Results' contains a plot of the individual study results grouped by treatment comparisons. Observe how the 3-arm studies appear in each of the different treatment comparisons.



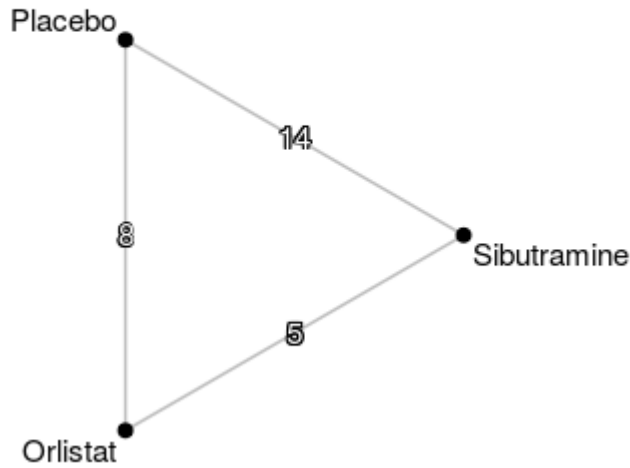
Question: What conclusions would you make from observing this plot?

Answer:

All studies consistently favoured Sibutramine to be more effective than Placebo, and the majority of studies favoured Orlistat to be more effective than Placebo with varying degrees of uncertainty. Two out of the five studies favoured Sibutramine when compared to Orlistat and the rest showed no difference in effectiveness between the two active treatments.

- vi) Click on the '1b. Network Plot' tab and you will see a network diagram displaying the 3 treatments included in the analysis together with the numbers along the lines indicating the number of trials comparing the treatments defined at either end of the line. For example, there are 5 trials comparing Orlistat and Sibutramine, which agrees with the plot of individual study results presented on the '1a. Study Results' tab.

Network plot of all studies



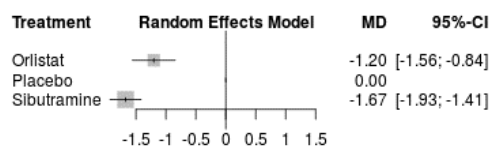
vii) The results of the frequentist network Meta-analysis can be observed by first clicking on the '2. Frequentist network meta-analysis' tab followed by the '2a. Forest plot' tab where the results are presented for each treatment compared to Placebo.

Question: Interpret the results

Answer:

Both Orlistat and Sibutramine are more effective at reducing weight than Placebo at the 5% significance level (i.e. the 95% confidence intervals are below zero).

Results for all studies



viii) The next tab, '2b. Comparison of all treatment pairs', contains three aspects of information:

- Treatment ranking: the best treatment is at the top left corner of the diagonal while the worst treatment is at the bottom right corner.
- Above the leading diagonal are the relative treatment effects from pairwise estimate (direct evidence only)
- Below the leading diagonal are estimates from network meta-analysis (both direct and indirect evidence)

Question: What is the relative effectiveness between Sibutramine and Orlistat?

Answer:

The network estimate suggests that Sibutramine is more effective than Orlistat at reducing weight at the 5% significance level.

Relative treatment effects in ranked order for all studies

Sibutramine	-0.48 [-0.98; 0.02]	-1.70 [-1.96; -1.43]
-0.47 [-0.85; -0.09]	Orlistat	-1.19 [-1.59; -0.79]
-1.67 [-1.93; -1.41]	-1.20 [-1.56; -0.84]	Placebo

- ix) The '2c. Inconsistency' tab contains the results of assessment of inconsistency for all studies. It shows the estimates from network (direct and indirect combined), direct, and indirect evidence. It also shows the difference between the direct and indirect estimate, its 95% confidence intervals, and p value.

Question: Is there any evidence for inconsistency?

Answer:

The estimates from the direct and indirect are consistent – we accept the null hypothesis of consistency.

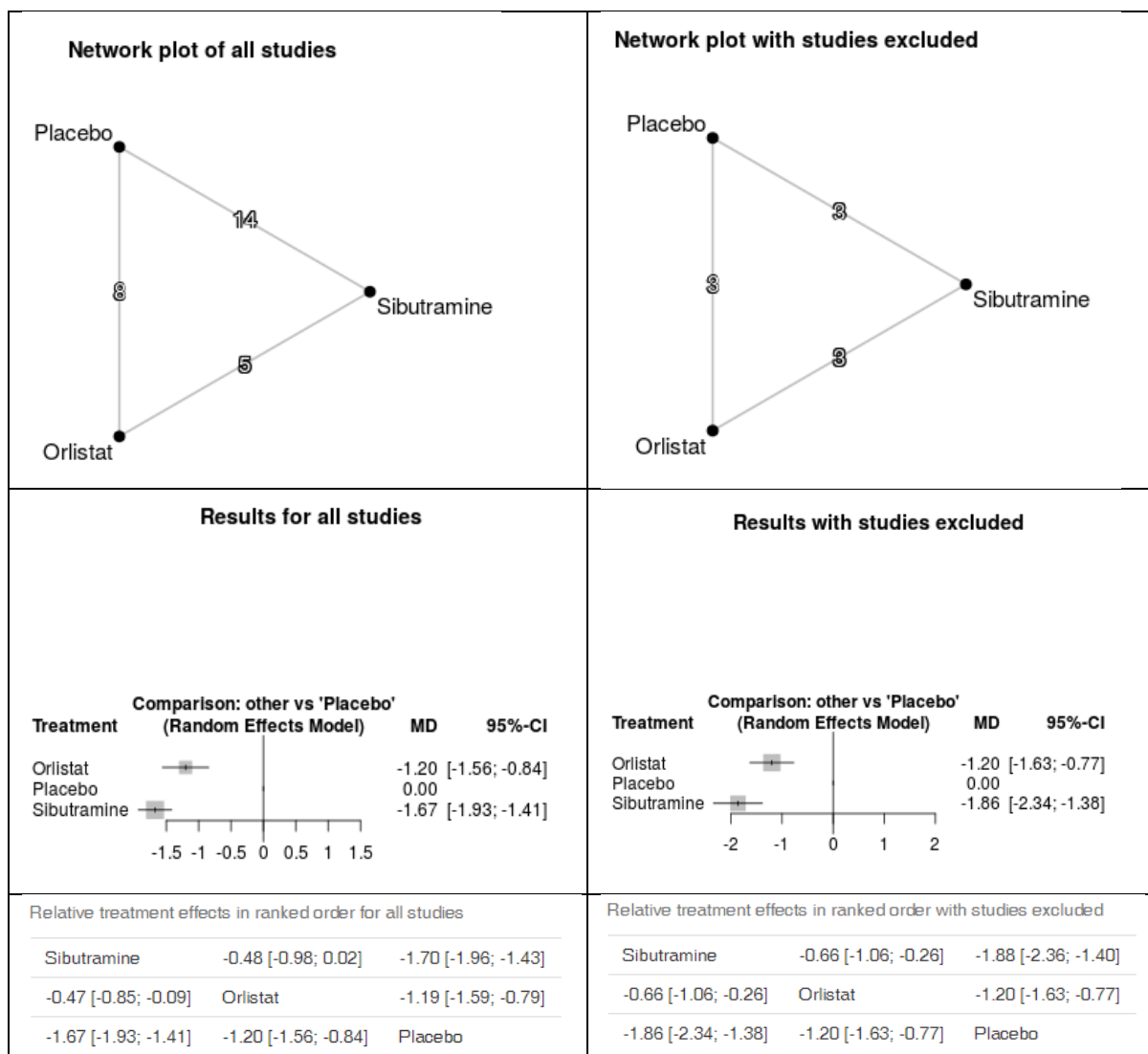
- x) It is easy to exclude studies in *Metalnsight* and to examine the influence this has on the overall results of the network meta-analysis. On the left-hand-side of the screen is a list of all the studies loaded into the App with radial buttons to select those studies you may want to exclude in a sensitivity analysis.

Question: Keeping only the 3-arm trials (i.e. those studies comparing the 3 treatments of interest directly), observe how the results presented on the following tabs change: 'Network Plot', 'Forest Plot', and 'Comparison of all treatment pairs'.

Answer:

Despite removing 18 of the 21 studies from the analysis, the results are similar leading to similar conclusions regarding the most effective treatment.

Including all studies	Including only 3-arm trials
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PART TWO:

In Part One, we kept the analysis simple by including only comparisons between the main three treatments of interest – Orlistat, Sibutramine and Placebo. We are now going to include:

- Further arms for two of the studies included in the simplified analysis that administered different treatments
 - Further studies that compare additional treatments that connect to the network
- i) Download the full data from the CRSU website:
<http://www.nihrcrsu.org/workshops/cochransymposium2019/>
 The data file, named 'Data_full.csv', and the treatment label file, named 'labels_full.txt', contain the complete data and the complete list of treatment labels, respectively.
 - ii) Upload the new dataset into *Metalnsight* (as outlined in Part One) and copy and paste the complete list of treatment labels.

- iii) Note the new comparisons are included in the '1a. Study Results' tab and observe the new network displayed in the '1b. Network Plot' tab. In particular, it is important to confirm that all the new treatments are connected to the network.

Question: Interpret the results on the '2a. Forest Plot' tab. Is a different treatment now estimated to be the most effective?

Answer:

All active treatments are estimated to be more effective than Placebo. Rimonbant is estimated to be the most effective treatment despite the relatively small amount of evidence (1 trial, see the '1b. Network Plot' tab) and correspondingly uncertain treatment effect estimate. Caution is required when interpreting ranks ('2b. Comparison of all treatment pairs' tab) as it does not take uncertainty into account.