Running meta-analyses with miniMeta

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Introduction

miniMeta is a shiny web application that makes it easy to run meta-analyses, without having any familiarity with R and its console. It is intended for use by non-statistical colleagues, or as educational tool. It is also intended to help guideline developers using the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluations) combine evidence and quickly fill their SoF (Summary of Findings) tables.

miniMeta can be run locally from an R installation, or fully online from a shiny server. It provides a "live" web interface where the meta-analysis is automatically updated as data are entered or options are adjusted. It can save (export) the results into files (RDS files) which can be later loaded (imported) to miniMeta, or also further processed in R if more detailed analyses are required.

Under the hood miniMeta relies on the meta package for R, and can be thought of as a graphical front-end for it. Analysis and plotting is done by functions from meta, in particular `metabin()`, `metagen()` and `forest.meta()`; see the associated function documentation for details.

How to install and run locally

Open R, install package `devtools` if you don't already have it, and then use `install_github()` to install the miniMeta package from GitHub:

```
install.packages("devtools")
devtools::install_github("thlytras/miniMeta")
```

This will bring in from CRAN all required dependencies if not already installed, such as packages shiny, meta and readxl.

In order to run miniMeta, load the package with `library()` and launch it with `miniMeta()`:

```
library(miniMeta)
miniMeta()
```

This will run miniMeta in a new browser window.

To install in a Shiny server for running over a network, first install the miniMeta R package, and then create an `app.R` file with just the following line:

```
miniMeta::miniMeta()
```

Put it in the appropriate place on your webserver (e.g. nginx), and off you go.

Using miniMeta

At the top of the miniMeta window, there are three tabs named "RCT module", "Observational studies module" and "Tools" respectively. Click one of the first two if you want to run a meta-analysis of Randomized Controlled Trials (RCTs) or observational studies. In the "Tools" tab there is a suite of small tools with which to perform various associated calculations.

Randomized Controlled Trials (RCT) module

At the top, there are buttons "Import meta-analysis" and "Export meta-analysis". Click "Export meta-analysis" to save the current meta-analysis (including dataset, analysis options and plot options) as an RDS file. This can be loaded later into miniMeta by clicking "Import meta-analysis".

The data are input on the left section of the page, and results are output on the right section. Options for the analysis are also set on the left section, whereas options for the forest plot are set on the right section.

Input section (left side)

Data can be input in two ways: by hand at the provided table widget, or loaded from an Excel spreadsheet. The Excel file must have the exact same layout as the table widget: each row represents one study, the first column holds the study labels, followed by the number of events (number of participants with the outcome) and total number of participants randomized in the intervention arm, the number of events and participants randomized in the control arm, and optionally a column defining subgroups for a subgroup analysis. If data are entered manually, then the meta-analysis and the forest plot on the right are updated automatically with each complete row entered. If a row is incomplete or the data make no sense (for example, more events than participants randomized) no forest plot is drawn. Click "Add rows" to insert more rows in the table widget, or "Clear empty rows" to clear all rows that are empty, except the last one (there is always a blank row at the bottom in order to fill in more data).

Click the "Save to Excel" button to save the dataset as an Excel spreadsheet. Only the dataset is saved; in contrast, the "Export meta-analysis" button saves everything (dataset, analysis options, plot options, and the entire meta-analysis object) in an RDS file that can be imported in miniMeta, or further processed in R.

By clicking the "Show analysis options" checkbox, a suite of options appear that determine how the meta-analysis is conducted (see the documentation of the `metabin()` function in package meta for full details). A common-effects or random-effects model can be specified, or both. There is a choice of different effect measures (Relative Risk, Odds Ratio, Risk Difference and Arcsine Difference), methods for pooling studies (Mantel-Hanszel, Inverse Variance and Peto) and heterogeneity estimators for the random-effects model (the default being the standard DerSimonian-Laird estimator). The Hartung and Knapp correction can be selected, as well as the type of continuity correction for study arms with zero events, with a "treatment arm continuity correction" (TACC) being the default. More options may be added in the future. With every change in these analysis options, the meta-analysis is automatically updated and a new forest plot is redrawn.

Output section (right side)

The right section of the miniMeta window is where all the output appears. There are several tabs: "Forest plot", "Plot options", "GRADE output" and "Help".

On the "Forest plot" tab, the forest plot appears automatically every time the input data or the analysis options are modified. Click the "Download plot" button to download the forest plot as an image file.

On the "Plot options" tab, every aspect of the forest plot can be customized as desired. The options are conceptually organized in four sections: "Download options", "Content options", "Formatting options" and "Advanced options". Click on the corresponding checkbox for the options to appear. "Download options" determine what kind of image file is downloaded when clicking the "Download plot" button (pdf, ps, tiff or png), its dimensions (in inches), its resolution in dots per inch (dpi - only for bitmap-type images, i.e. tiff or png) and factors such as line width, spacing (between study rows) and pointsize (affecting the size of text).

"Content options" control what is shown in the forest plot and what is not, e.g. absolute numbers per study arm, weights, heterogeneity statistics, etc. "Formatting options" affect various aesthetical characteristics of the forest plot or the funnel plot (see below).

Finally, "Advanced options" provides a powerful interface (for advanced users) to control any aspect of the forest plot, by specifying a comma-separated list of arguments that are passed to the `forest.meta()` method. Any argument listed in the function documentation of `forest.meta()` can be specified in the input box, and these *override* any other options set in miniMeta. For example, if `col.diamond="red"` is entered in the input box, the diamond illustrating the pooled effect measure is painted red. This interface allows customizing the forest plot in ways that go beyond the options provided in miniMeta, but still without resorting to the R console.

The "GRADE output" tab provides results for a "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) Summary of Findings (SoF) table. When filling in such a table, each row corresponds to one meta-analysis of RCTs for a single outcome, and in the five rightmost columns one puts the Event Rate for the control and intervention groups, the pooled relative effect (usually a Risk Ratio), the absolute risk in the control group (per 1000 patients) and the absolute Risk Difference in the intervention group. miniMeta provides these information automatically in the "GRADE output" tab.

The "Funnel plot" tab provides a funnel plot to assess publication bias or small study effects. The results for the Begg & Mamzudar and Egger tests are provided below the funnel plot, as well as a L'Abbe plot.

The last tab, "Help", includes some brief usage help to get you started with miniMeta.

Observational studies module

The observational studies module roughly follows the interface of the RCT module, and most of the descriptions there apply here as well, but with some adaptations for the meta-analysis of observational studies. Again the input data and analysis options are entered on the left side, with all output on the right side. "Import meta-analysis"/"Export meta-analysis" buttons can be found at the top.

Input section (left side)

Input (study) data can again be entered via an Excel file or on the table widget. However, the columns are different. The first column again contains the study labels, but the next columns contain the study effect point estimate, the lower/upper limits of the 95% Confidence Interval (95% CI), and the standard error (SE) of the effect. A final grouping column is available, if subgroup analyses are desired.

The table widget also operates in a slightly more complex way than in the RCT module. Studies normally report the point estimate of the effect and the associated 95% CI; however, the calculations in a meta-analysis of observational studies involve the point estimate and its *standard error*, which can be *derived* from the confidence interval. As a result, while the effect measure and its 95% CI are entered in the table widget, the SE is automatically calculated and filled in the respective table cell. SE always remains in sync with the provided 95% CI, unless the "Auto-calculate SE" checkbox is unchecked; then a SE can be entered manually (but, if blank, will still be automatically calculated based on the 95% CI). Potential problems with the data entered, such as SE that do not match the 95% CI or a CI that are not symmetrical, are indicated with a message that appears just below the table widget.

Below the table widget is a drop-down menu there the type of effect measure is selected (Relative Risk, Odds Ratio, Risk Difference or Arcsine difference). This determines what kind of measure the "effect" and the "SE" column represent. If the effect measure is the Relative Risk or Odds Ratio, then the SE column represents the standard error of the *log* Relative Risk or *log* Odds Ratio.

Click "Show analysis options" to adjust further options for the meta-analysis (see the documentation of the `metagen()` function in package meta for full details). A common-effects or random-effects model can be specified, or both. Different heterogeneity estimators can be chosen for the random-effects model (the default being the standard DerSimonian-Laird estimator), and the Hartung and Knapp correction can be selected as

well. With every change in these analysis options, the meta-analysis is automatically updated and a new forest plot is redrawn.

Output section (right side)

The output section of the Observational studies module, on the right side of the miniMeta window, is very similar to that of the RCT module.

On the "Forest plot" tab, the forest plot appears automatically every time the input data or the analysis options are modified. Click the "Download plot" button to download the forest plot as an image file. Note that the 95% CIs on the forest plot *may not exactly correspond* to those on the input table widget. This is because what is analysed is the effect and its standard error, and the 95% CIs are recalculated based on that.

On the "Plot options" tab, every aspect of the forest plot can be customized as desired. The four sections ("Download options", "Content options", "Formatting options" and "Advanced options") are the same as in the RCT module. Some items in the "Content options" section that may not apply to observational studies have been omittted.

The "GRADE" output tab is again the same as in the RCT module, with one difference: an input field is provided to specify a baseline risk. This is because, in contrast to a meta-analysis of RCTs, the baseline risk cannot be estimated from the study data and must be plugged in separately. The "Funnel plot" section does not include a L'Abbe plot, as these are not applicable to observational studies.

Tools

At the "Tools" tab, a suite of small additional tools can be found that are useful when performing a meta-analysis. Currently this contains just two tools: one that implements the Bucher method for adjusted indirect comparisons, and one that makes optimal information size (OIS) calculations (see the GRADE handbook for details).

Bucher method tool

This tools implement the Bucher method for adjusted indirect comparisons. It utilizes two *pooled* effect measures, comparing two outcomes against a common third outcome (outcome A vs outcome C, and outcome B vs outcome C). Then a comparison of A vs B can be performed by taking the *difference* of the two effect point estimates, and the *sum* of their variances (squared standard errors). Fill in the point estimate and 95% CI lower/upper limits for the two pooled effect estimates (A vs C, and B vs C), and the results will appear on the right side of the miniMeta window.

Optimal Information Size calculator

Fill in the appropriate information on the left side, depending on whether the study under consideration uses a binary or a continuous outcome. For a binary outcome, one needs to provide anticipated event rates for the control and intervention groups, or a control group event rate and a Relative Risk reduction (RRR, %). For a continuous outcome, the anticipated mean difference and standard deviation must be provided. In both cases, one can adjust the type I error rate (alpha), the power (1 - beta) and the group size ratio; defaults are alpha = 0.05, power = 80% and n1/n2 = 1. Results appear on the right side.

Other miniMeta features

Import/export functionality

In both the RCT module and Observational studies module, there are buttons for importing from / exporting to an RDS file. An RDS file holds a single serialized R object, and can be read into R using the console. The exported objects are of class 'miniMeta', and are essentially a list with four elements: 'data', 'meta', 'analysisOptions' and 'plotOptions'. Element 'data' contains the study data, as an R data.frame. Element

'meta' contains the meta-analysis (an object of class 'meta'). The other two elements are named lists containing all analysis and plot options.

Objects of class 'miniMeta' can be further processed in R, or (when stored in an RDS file) can be imported back into miniMeta. They can also be converted into an R source code format using the `as.source()` function of the miniMeta package, and can be saved as an R script with something like `writeLines(as.source(m), "analysis.R")` (m is the 'miniMeta' class object). Such a script contains (a) the data, (b) the command to run the meta-analysis, and (c) the command to make the forest plot. It allows you to reproduce the meta-analysis, or extend it further into more complex analyses.

Settings storage/retrieval

In the RCT and observational studies module, at the top right corner there is a "Settings" button that shows a dropdown menu when clicked. This can be used to store **all** options set (in both modules, both analysis and plot options), so that they can be used again when working with the same computer, or so that they can be shared with a colleague who works on the same project.

The settings can be stored in two places; either in the browser, using a cookie (cookies must be enabled for this to work), or in an RDS file. Click "Save settings to file" or "Load settings from file" in the menu to save settings into / load settings from and an RDS file. Note that this is not the same RDS file used when exporting/importing a meta-analysis; instead of a 'miniMeta' class object, these files contain a list of all the settings.

In similar fashion, click "Save settings to browser" to store the settings in a browser cookie. A confirmatory message "Stored miniMeta settings in browser" appears for a few seconds. When launching miniMeta in the future, these settings will automatically be loaded, with a confirmatory message "Restored miniMeta settings from browser" appearing again on the top right corner. If altered, they can be loaded again manually out of the stored browser cookie by clicking "Load settings from browser". Click "Clear settings from browser" to remove the cookie from your browser.