

Appendix A

Further Information on R

Many valuable information and files for installation of R can be found on the Comprehensive R Archive Network (CRAN). The user is advised to choose a mirror of CRAN which is close to the current location. A list of all mirrors is available on the website <http://cran.r-project.org/mirrors.html>. At the time of writing about 100 mirrors from 48 countries exist.

On CRAN, a general R FAQ [3] and FAQs for Mac OS and Windows are provided.

Furthermore, the following manuals are available on CRAN.

1. An Introduction to R
2. R Data Import/Export
3. R Installation and Administration
4. Writing R Extensions
5. The R language definition (draft)
6. R Internals
7. The R Reference Index

For beginners, manuals 1 and 2 are of most interest.

A.1 Installation of R

Precompiled binary distributions of R are available on CRAN for the major operation systems Linux, Windows and Mac OS. Furthermore, R can be configured and built by the user on many Unix-like operation systems [3].

In order to install R for Windows or Mac OS, go to your favourite CRAN mirror, open the webpage *Download R for Windows* or *Download R for (Mac) OS X* and download the EXE- or PKG-file of the precompiled binary distribution, respectively.

For Debian, Ubuntu, Red Hat and SuSE Linux, instructions to install precompiled binaries are available on your favourite CRAN mirror on the webpage *Download R for Linux*.

For all other operation systems, the source code can be downloaded from any CRAN mirror.

A.2 Importing Data into R

The R manual ‘R Data Import/Export’ available on CRAN is obviously a good starting point for information on data import. Furthermore, a Use-R! book on data manipulation has two chapters on reading and writing data [11].

A.2.1 Import Text Files

Throughout the book we have used the `read.csv` to import data in R from a text file. This function expects that fields are separated by a comma whereas a dot is used as decimal point. Some information on this and similar R functions is given in the following listing.

R function	Separator (argument <code>sep</code>)	Decimal point (argument <code>dec</code>)
<code>read.csv</code>	Comma	Dot
<code>read.csv2</code>	Semicolon	Comma
<code>read.delim</code>	Tabulator	Dot
<code>read.delim2</code>	Tabulator	Comma
<code>read.table</code>	White Space	Dot

Note, these functions only differ in default values for `sep` and `dec` as well as other arguments (see shared help page for these commands).

The following function calls all result in the same dataset.

```
> rd1 <- read.csv("dataset01.csv", as.is=TRUE)
> rd2 <- read.csv2("dataset01.csv", as.is=TRUE,
+                 sep=";", dec=".")
> rd3 <- read.delim("dataset01.csv", as.is=TRUE,
+                  sep=";", dec=".")
> rd4 <- read.delim2("dataset01.csv", as.is=TRUE,
+                   sep=";", dec=".")
> rd5 <- read.table("dataset01.csv", as.is=TRUE,
+                  sep=" ", dec=".", header=TRUE)
```

which can be checked using the following commands

```
> all.equal(rd1, rd2)
[1] TRUE
```

```
> all.equal(rd1, rd2)
[1] TRUE
> all.equal(rd1, rd3)
[1] TRUE
> all.equal(rd1, rd4)
[1] TRUE
> all.equal(rd1, rd5)
[1] TRUE
```

A.2.2 Import Data from RevMan 5

It is possible to export the analyses data from RevMan 5 [13] to a CSV-file (Comma Separated Values). Whereas it is in principle possible to import this CSV-file in R using any of the above-mentioned R functions, a much more convenient way to import these data is using the `read.rm5` function from R package **meta**.

The following steps are necessary in RevMan 5 to create the CSV-file:

1. Open the Menu *File* → *Export* → *Data and analyses*.
2. Click ‘Next’ at the bottom of the dialog box *Which analyses would you like to export?*
3. Select all items but ‘Risk of bias tables’ in the dialog box *Which fields do you want to include?* and click ‘Next’.
4. Click ‘Finish’ and save the CSV-file.

The resulting CSV-file can be imported in R using the `read.rm5` function.

```
> examples <- read.rm5("Examples from Meta-Analysis with R.csv",
+                      numbers.in.labels=FALSE)
> dim(examples)
[1] 31 54
> class(examples)
[1] "rm5" "data.frame"
```

The `read.rm5` function creates a data frame with the additional class `rm5`. This data frame contains 31 observations, i.e. studies which are included in meta-analyses, and 54 variables with detailed information to conduct the meta-analyses. The following command prints some information for this data frame.

```
> examples[, 1:6]
  comp.no outcome.no group.no studlab year event.e
1      1      1      1      Boner 1988 1988      0
2      1      1      1      Boner 1989 1989      0
*** Output truncated ***
17     1      1      1      Todaro 1993 1993      0
18     2      1      1      De Souza  NA     14
*** Output truncated ***
31     2      1      1      Vitolo   NA     35
```

The first 17 observations contain data from the bronchoconstriction meta-analysis (see Fig. 1.2) and the following 14 observations from the high-dose chemotherapy meta-analysis (see Fig. 3.1).

The `metacr` function can be used to conduct a meta-analysis for the RevMan 5 data.

```
> args(metacr)
function (x, comp.no = 1, outcome.no = 1, method, sm,
  level = .settings$level, level.comb = .settings$level.comb,
  comb.fixed, comb.random,
  hakn = FALSE, method.tau = "DL", tau.common = FALSE,
  prediction = .settings$prediction,
  level.predict = .settings$level.predict, swap.events,
  logscale, backtransf = .settings$backtransf,
  title, complab, outclab, keepdata = .settings$keepdata,
  warn = FALSE)
NULL
```

Argument `x` is a RevMan 5 object and arguments `comp.no` and `outcome.no` define which meta-analysis to conduct. The other arguments can be used to conduct a meta-analysis with different setting than in RevMan 5.

By default, the `metacr` function conducts a meta-analysis for the first comparison and first outcome, i.e. data from the bronchoconstriction meta-analysis in our example file. In order to do a meta-analysis for the high-dose chemotherapy data, we have to specify arguments `comp.no` and `outcome.no`.

```
> mcl.cr <- metacr(examples)
> mbl.cr <- metacr(examples, 2, 1)
```

Based on the CSV-files for each meta-analysis separately, we could conduct these meta-analyses in the following way.

```
> # 1. Read in the data
> data1 <- read.csv("dataset01.csv", as.is=TRUE)
> # 2. Conduct meta-analysis
> mcl.md <- metacont(Ne, Me, Se, Nc, Mc, Sc,
+                   data=data1, studlab=paste(author, year),
+                   comb.random=FALSE)
> # 3. Read in the data
> data7 <- read.csv("dataset07.csv")
> # 4. Conduct meta-analysis
> mbl.rr <- metabin(Ee, Ne, Ec, Nc, data=data7, studlab=study,
+                  comb.random=FALSE)
```

These meta-analyses will give the same results as those based on the CSV-file from RevMan 5 and the `metacr` function. We only show results for Example 2.1.

The class of the R objects are identical

```
> class(mcl.cr)
[1] "metacont" "meta"
> class(mcl.md)
[1] "metacont" "meta"
```

as well as the meta-analytical results

```
> print(summary(mcl.cr), digits=2)
Review:      Examples from Meta-Analysis with R
Comparison:  Chapter 2 - Meta-Analysis with Continuous Outcomes
Outcome:     Example 2.1 - Nedocromil sodium for bronchoconstriction
```

```
Number of studies combined: k=17
```

```

              MD              95%-CI      z  p.value
Fixed effect model -15.51 [-17.84; -13.18] -13.05 < 0.0001
```

```
Quantifying heterogeneity:
```

```
tau^2 = 2.4374; H = 1.05 [1; 1.35]; I^2 = 8.9% [0%; 45.3%]
```

```
Test of heterogeneity:
```

```

  Q d.f.  p.value
17.57  16   0.3496
```

```
Details on meta-analytical method:
```

```
- Inverse variance method
```

```
> print(summary(mcl.md), digits=2)
```

```
Number of studies combined: k=17
```

```

              MD              95%-CI      z  p.value
Fixed effect model -15.51 [-17.84; -13.18] -13.05 < 0.0001
```

```
Quantifying heterogeneity:
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tau^2 = 2.4374; H = 1.05 [1; 1.35]; I^2 = 8.9% [0%; 45.3%]
```

```
Test of heterogeneity:
```

```

  Q d.f.  p.value
17.57  16   0.3496
```

```
Details on meta-analytical method:
```

```
- Inverse variance method
```

Only difference in the printout is a header giving details on the review, comparison, and outcome which is only printed for the meta-analysis conducted using the `metacr` function. However, we could add the header using arguments `title`, `complab` and `outclab` in the `metacont` function.

Another nice thing about using the `read.rm5` function is that we can conduct tests for small-study effects for all meta-analyses using a single command.

```
> metabias(examples)
Review:      Examples from Meta-Analysis with R
Comparison:  Chapter 2 - Meta-Analysis with Continuous Outcomes
Outcome:     Example 2.1 - Nedocromil sodium for bronchoconstriction
```

```
Linear regression test of funnel plot asymmetry
```

```
data:  ml
```

```
t = -1.1828, df = 15, p-value = 0.2553
alternative hypothesis: asymmetry in funnel plot
sample estimates:
      bias      se.bias      slope
-0.9571707  0.8092752 -11.0548678
```

```
*****
```

```
Review:      Examples from Meta-Analysis with R
Comparison:  Chapter 3 - Meta-Analysis of Binary Outcomes
Outcome:     Example 3.1 - Stem Cell Transplantation
```

Linear regression test of funnel plot asymmetry

```
data:  m1
t = 0.185, df = 12, p-value = 0.8564
alternative hypothesis: asymmetry in funnel plot
sample estimates:
      bias      se.bias      slope
0.16233218  0.87767199  0.09201333
```

A similar function is available to print a summary of all meta-analyses, i.e. the `summary.rm5` function.

A.3 R Packages for Meta-Analysis

In our book we primarily used the R packages **meta**, **metasens**, **netmeta**, **mvmeta** and **mada**. In this section we will give some information on other R packages for meta-analysis which are also available on CRAN. Furthermore, we would like to refer the reader to the CRAN ‘Task View on meta-analysis’ with short descriptions on available R packages for meta-analysis: <http://cran.r-project.org/web/views/MetaAnalysis.html>. We now briefly review some of the general meta-analysis packages and some recent network meta-analysis software developments.

A.3.1 General Purpose R Packages for Meta-Analysis

Besides the R package **meta** [8, 9], **metafor** [15] and **rmeta** [5] are two other general purpose R packages for meta-analysis providing the inverse variance and Mantel–Haenszel method. In addition, **metafor** provides the Peto method.

The following R code shows how to conduct a meta-analysis with a binary outcome using the `metabin` function from R package **meta**; by default risk ratio (see Sect. 3.1.2) and Mantel–Haenszel method (see Sect. 3.3.2) are used.

```
> # Make R package meta available
> library(meta)
```

```

Loading 'meta' package (version 4.0-2).
> # Do meta-analysis
> mbl.meta <- metabin(Ee, Ne, Ec, Nc, data=data7, studlab=study,
+                   comb.random=FALSE)

```

R code to conduct this meta-analysis with binary outcomes using the `rma.mh` function from R package **metafor** is given as follows.¹

```

> # Make R package metafor available
> library(metafor)
Loading 'metafor' package (version 1.9-5). For an overview
and introduction to the package please type: help(metafor).

```

Attaching package: 'metafor'

The following objects are masked from 'package:meta':

```

    baujat, forest, funnel, labbe, radial, trimfill

```

```

> # Do meta-analysis using default settings (numbers of events)
> mbl.metafor <- rma.mh(Ee, Ne-Ee, Ec, Nc-Ec,
+                   data=data7, measure="RR")
> # Do meta-analysis using same input as R function metabin
> mbl.metafor <- rma.mh(ai=Ee, nli=Ne, ci=Ec, n2i=Nc,
+                   data=data7, measure="RR")

```

You can safely ignore the warnings regarding R objects masked from R package **meta** as both R packages have been designed to work together. All masked functions act as wrapper functions for other functions in R packages **meta** and **metafor**, respectively. Note, we have to use argument `measure="RR"` as the default effect measure in the `rma.mh` function is the odds ratio.

The following R code can be used to conduct a meta-analysis using the Mantel-Haenszel method using the `meta.MH` function from R package **rmeta**.²

```

> # Make R package rmeta available
> library(rmeta)
Loading required package: grid
> mbl.rmeta <- meta.MH(Ne, Nc, Ee, Ec, data=data7,
+                   statistic="RR")

```

Again, we have to use an argument, here `statistic="RR"`, to specify the risk ratio as the default effect measure in the `meta.MH` function is the odds ratio.

First, we print the meta-analysis result of R object `mbl.meta` created with the R package **meta** using the `print.meta` function.

```

> print(summary(mbl.meta), digits=2)

```

¹If you did not already install R package **metafor** do so using R command `install.packages("metafor")`.

²In order to do these analyses you have to install R package **rmeta** using the command `install.packages("rmeta")`.

Number of studies combined: k=14

	RR	95%-CI	z	p.value
Fixed effect model	1.11	[1.04; 1.18]	3.2	0.0014

Quantifying heterogeneity:

$\tau^2 = 0.0079$; $H = 1.25$ [1; 1.71]; $I^2 = 35.6\%$ [0%; 65.9%]

Test of heterogeneity:

Q	d.f.	p.value
20.19	13	0.0906

Details on meta-analytical method:

- Mantel-Haenszel method

Next, we print the meta-analysis result of R object `mb1.metafor` created with the R package **metafor** using the `print.rma.mh` function.

```
> print(mb1.metafor, digits=2)
```

Fixed-Effects Model (k = 14)

Test for Heterogeneity:

Q(df = 13) = 20.19, p-val = 0.09

Model Results (log scale):

estimate	se	zval	pval	ci.lb	ci.ub
0.10	0.03	3.20	<.01	0.04	0.16

Model Results (RR scale):

estimate	ci.lb	ci.ub
1.11	1.04	1.18

Last, we print the meta-analysis result of R object `mb1.rmeta` created with the R package **rmeta** using the `print.meta.MH` function.

```
> print(mb1.rmeta)
```

Fixed effects (Mantel-Haenszel) Meta-Analysis

Call: meta.MH(ntrt = Ne, nctrl = Nc, ptrt = Ee, pctrl = Ec,
data = data7, statistic = "RR")

Mantel-Haenszel RR =1.11 95% CI (1.04, 1.18)

Test for heterogeneity: X²(13) = 20.19 (p-value 0.0906)

As we can see in the printouts, all R packages provide comparable outputs using different printing formats.

The `rma.uni` function from R package **metafor** can be used to do a meta-regression. Actually, the `metareg` function from R package **meta** calls this function internally. R package **metafor** also provides several functions for model diagnostics [15] which can be used with an R object generated with the `rma.uni` or `metareg` function.

A.3.2 R Packages to Conduct Network Meta-Analysis

Van Valkenhoef et al. [14] have published an R package **gemtc** that conducts network meta-analysis using a Bayesian hierarchical model.

A widely applied analysis method is the Bayesian approach, more specifically a Markov Chain Monte Carlo (MCMC) method [1, 2, 4, 6, 7]. It is implemented in special software such as WinBUGS [10]. We will not explain the Bayesian approach here. It is only noted that there exist a number of interfaces from R to WinBUGS and similar MCMC software, such as the R package **R2WinBUGS** [12]. These packages enable R users to manage their data in R such that they can be processed by the Bayesian software, using calls from the R environment.

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