

Meta Analysis with R

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INDEX OF LESSON 1

1. What is R
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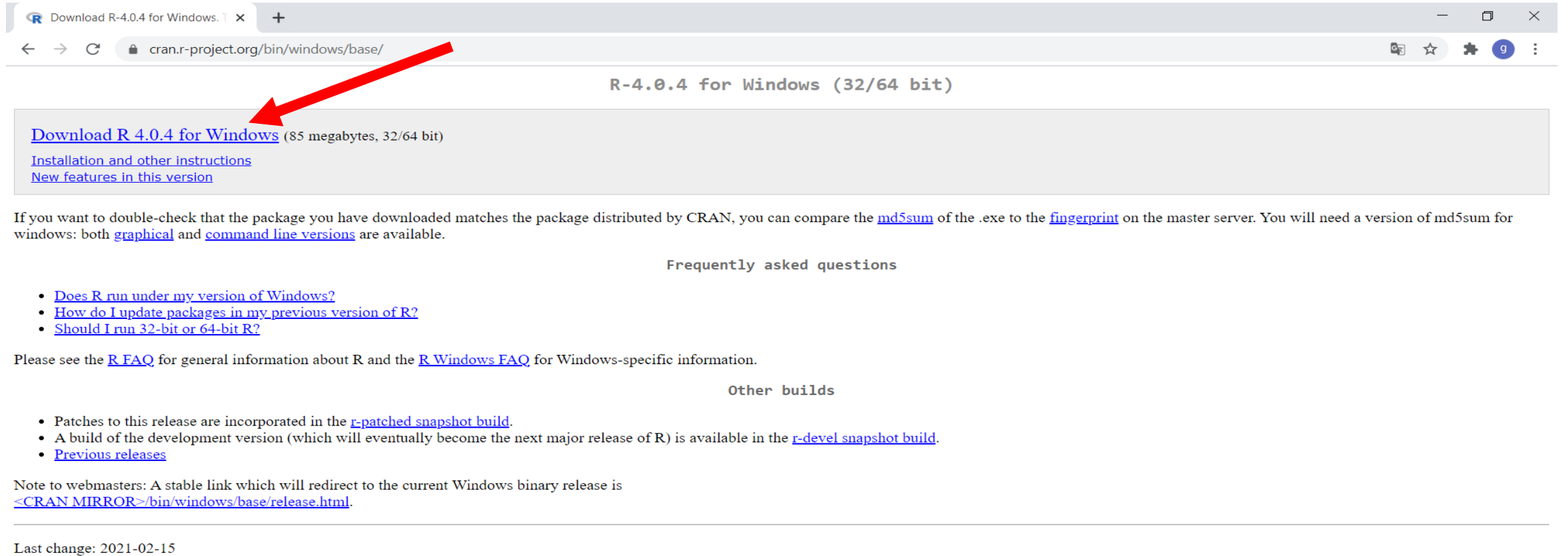
What Is R?

R is a language and environment for statistical computing and graphics.

R provides a wide variety of statistical (linear and nonlinear modelling, classical statistical tests, time-series analysis, classification, clustering, ...) and graphical techniques, and is highly extensible.

The S language is often the vehicle of choice for research in statistical methodology, and R provides an Open Source route to participation in that activity.

How We Can Install R?



The screenshot shows a web browser window with the address bar displaying `cran.r-project.org/bin/windows/base/`. The page title is "Download R-4.0.4 for Windows (32/64 bit)". A red arrow points to the link "Download R 4.0.4 for Windows (85 megabytes, 32/64 bit)". Below this link are two sub-links: "Installation and other instructions" and "New features in this version".

[Download R 4.0.4 for Windows](#) (85 megabytes, 32/64 bit)

[Installation and other instructions](#)

[New features in this version](#)

If you want to double-check that the package you have downloaded matches the package distributed by CRAN, you can compare the [md5sum](#) of the .exe to the [fingerprint](#) on the master server. You will need a version of md5sum for windows: both [graphical](#) and [command line versions](#) are available.

Frequently asked questions

- [Does R run under my version of Windows?](#)
- [How do I update packages in my previous version of R?](#)
- [Should I run 32-bit or 64-bit R?](#)

Please see the [R FAQ](#) for general information about R and the [R Windows FAQ](#) for Windows-specific information.

Other builds

- Patches to this release are incorporated in the [r-patched snapshot build](#).
- A build of the development version (which will eventually become the next major release of R) is available in the [r-devel snapshot build](#).
- [Previous releases](#)

Note to webmasters: A stable link which will redirect to the current Windows binary release is [<CRAN MIRROR>/bin/windows/base/release.html](#).

Last change: 2021-02-15

R-4.0.4 for Windows (32/64 bit)

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[Installation and other instructions](#)

[New features in this version](#)

If you want to double-check that the package you have downloaded matches the package distributed by CRAN, you can compare the [md5sum](#) of the .exe to the [fingerprint](#) or [command line versions](#) are available.

Frequently asked questions

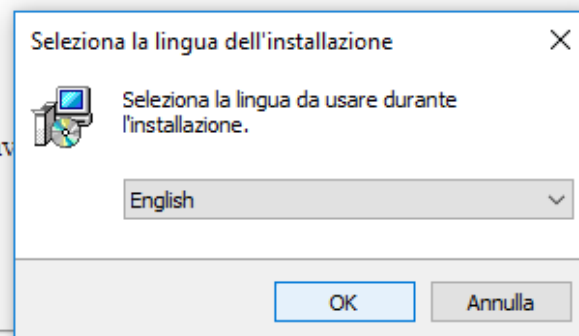
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- A build of the development version (which will eventually become the next major release of R) is available at [development version](#).
- [Previous releases](#)

Note to webmasters: A stable link which will redirect to the current Windows binary release is <<CRAN MIRROR>/bin/windows/base/release.html>.

Last change: 2021-02-15



R-4.0.4 for Windows (32/64 bit)

[Download R 4.0.4 for Windows](#) (85 megabytes, 32/64 bit)

[Installation and other instructions](#)

[New features in this version](#)

If you want to double-check that the package you have downloaded matches the [source](#) and [command line versions](#) are available.

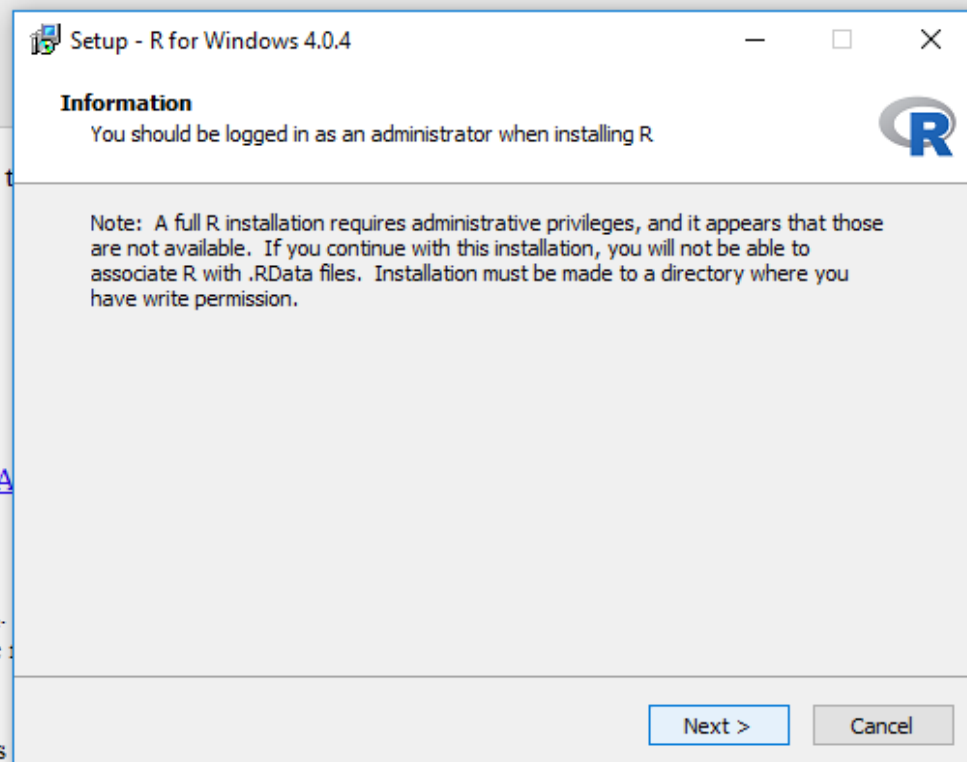
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- [Previous releases](#)

Note to webmasters: A stable link which will redirect to the current Windows [CRAN MIRROR](#) [/bin/windows/base/release.html](#).

Last change: 2021-02-15



R-4.0.4 for Windows (32/64 bit)

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[Installation and other instructions](#)

[New features in this version](#)

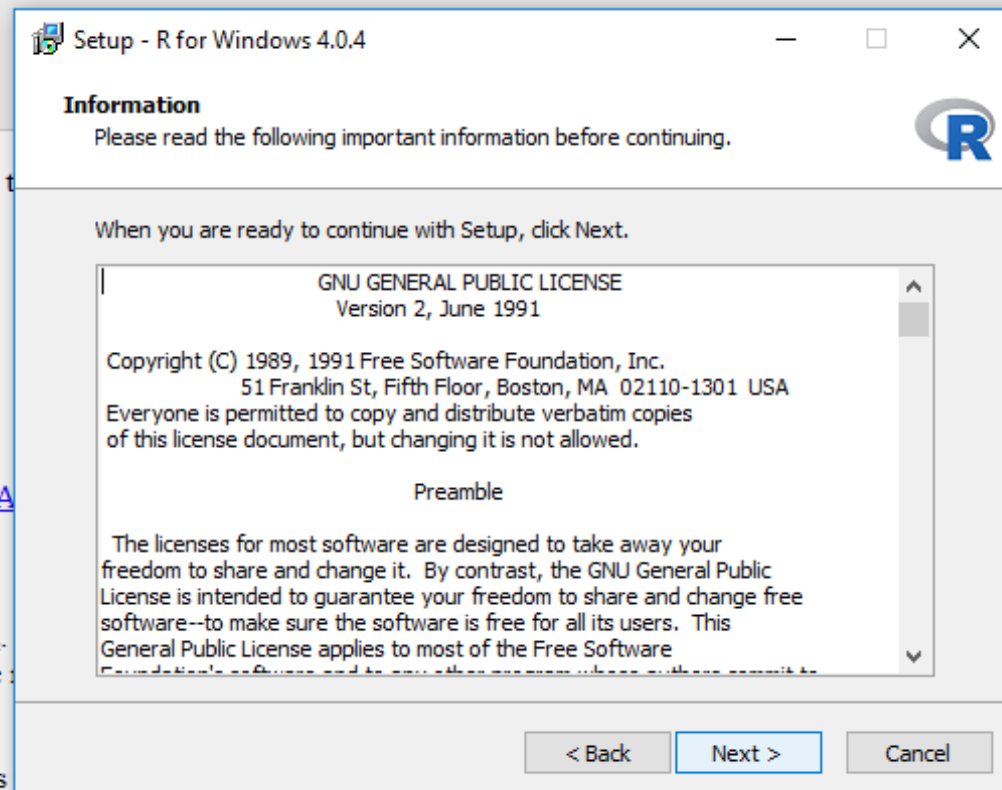
If you want to double-check that the package you have downloaded matches the [fingerprint](#) on the [CRAN MIRROR](#) and [command line versions](#) are available.

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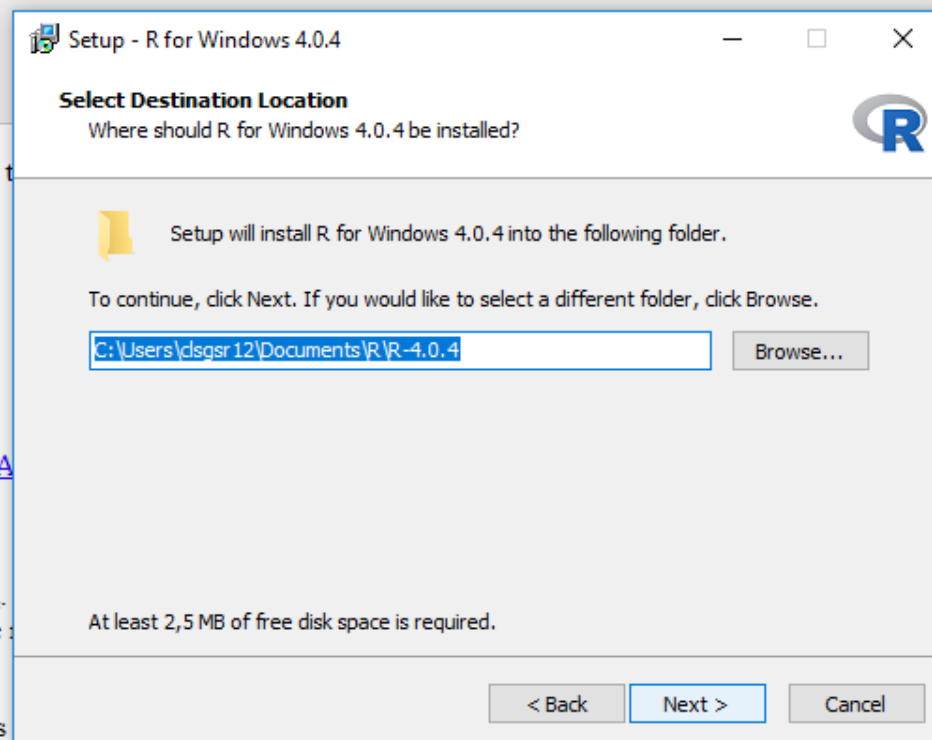
If you want to double-check that the package you have downloaded matches the [R Windows FAQ](#) and [command line versions](#) are available.

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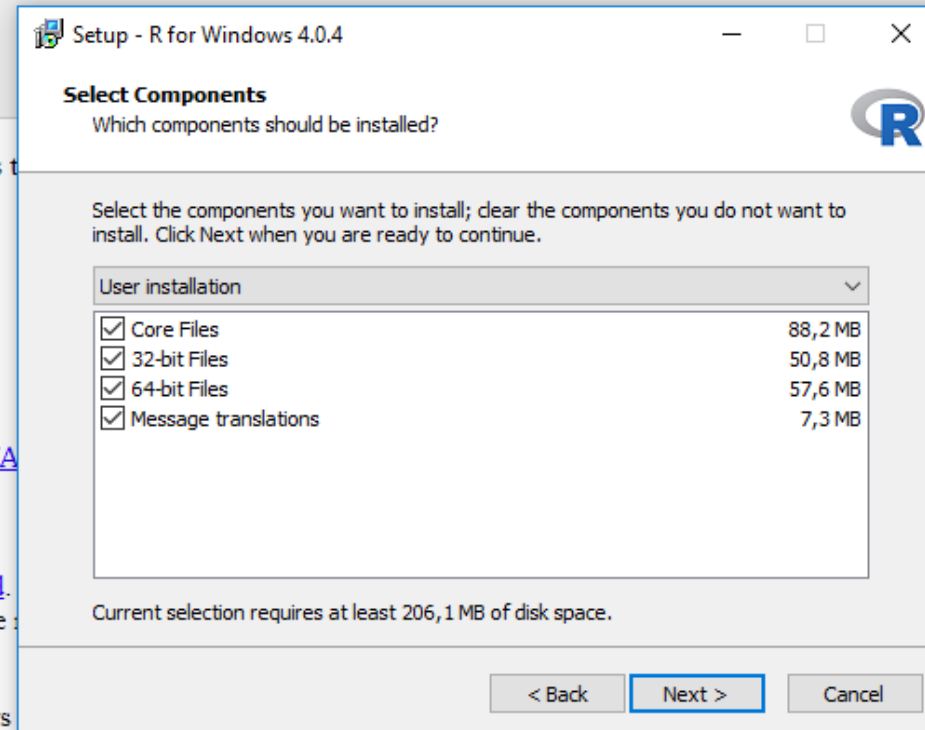
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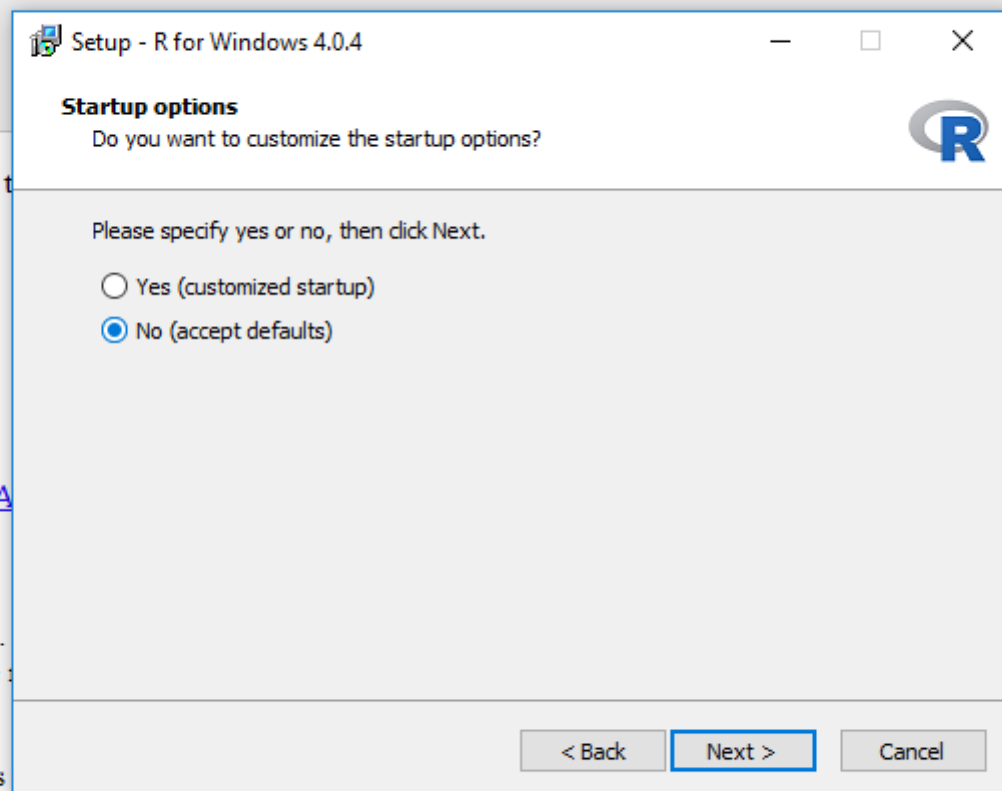
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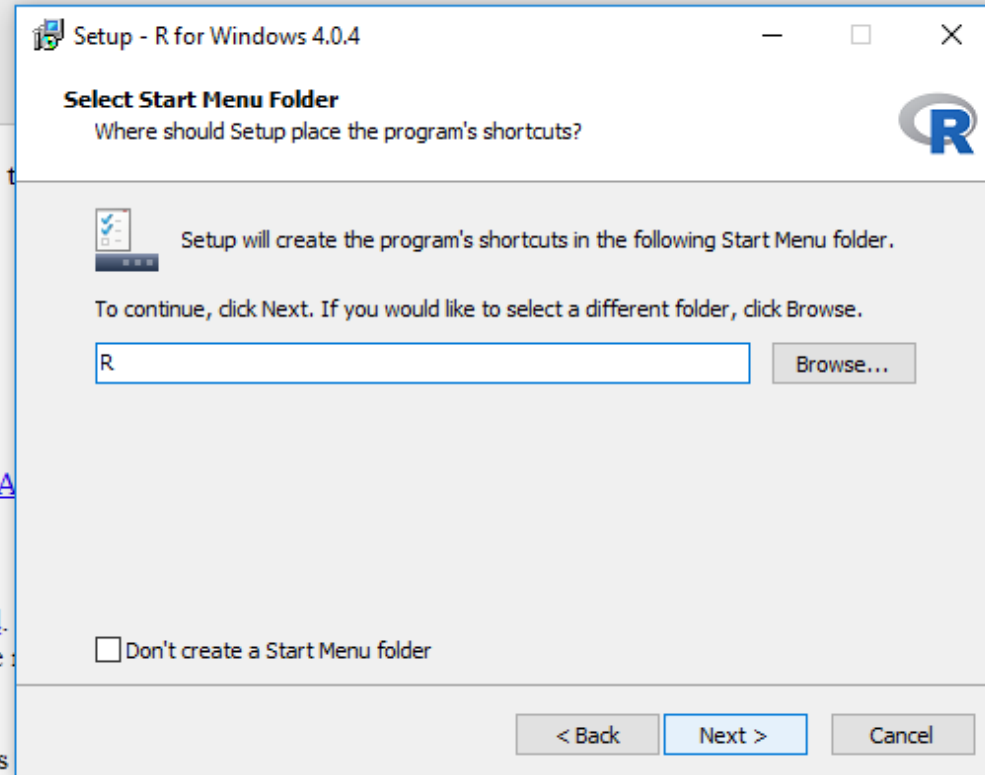
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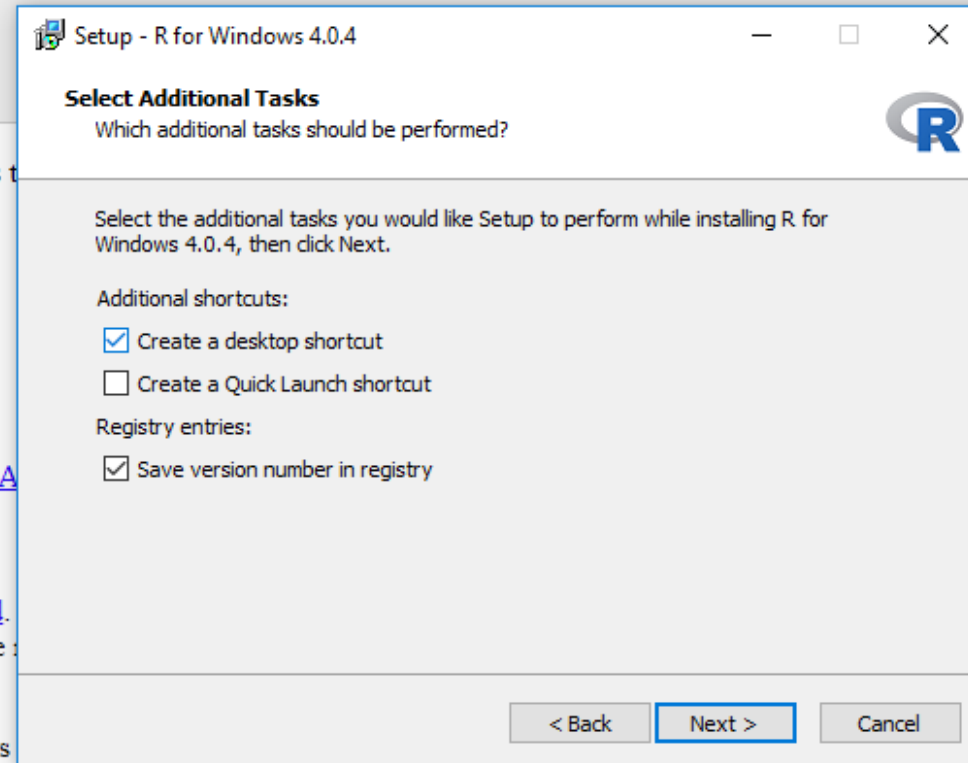
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How R Works?

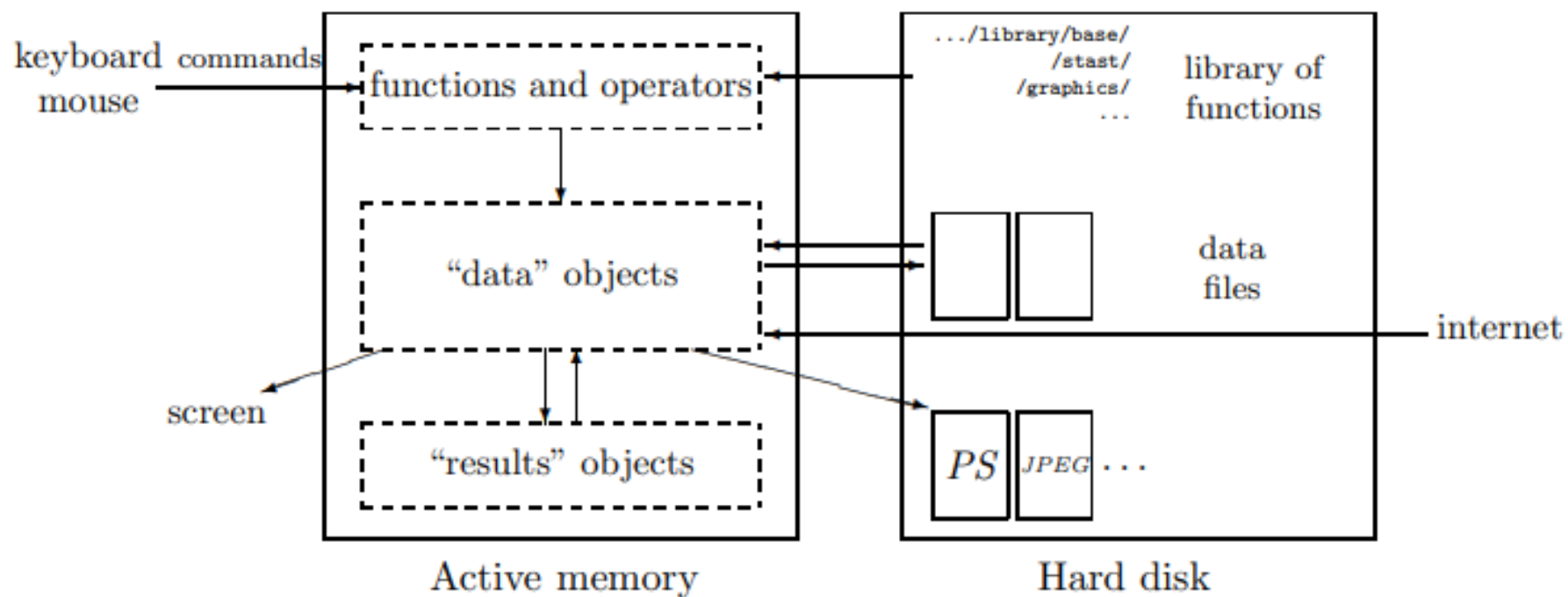


Figure 1: A schematic view of how R works.

Assignments

R, like other computer languages, has *symbolic variables*, that is names that can be used to present values. To assign the value 2 to the variable x,

```
>x<-2
```

The two characters `<-` should be read as a single symbol: an arrow pointing to the variable to which value is assigned. This is known as the *assignment operator*.

PACKAGES IN R

The following table lists the standard packages which are distributed with a base installation of R. Some of them are loaded in memory when R starts; this can be displayed with the function `search`:

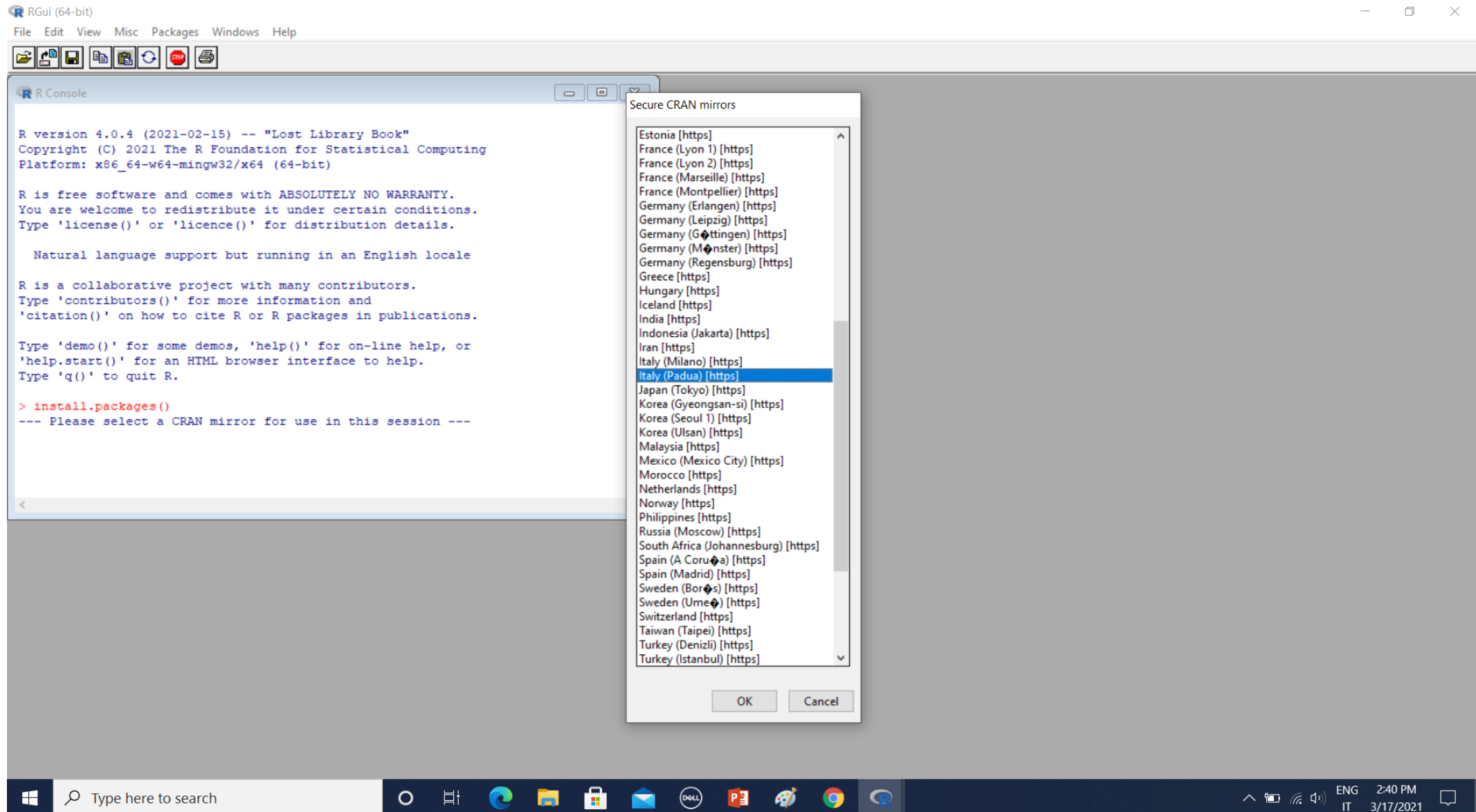
```
> search()  
[1] ".GlobalEnv"          "package:stats"      "package:graphics"  
[4] "package:grDevices"   "package:utils"      "package:datasets"  
[7] "package:methods"     "Autoloads"          "package:base"
```

Package	Description
base	base R functions
datasets	base R datasets
grDevices	graphics devices for base and grid graphics
graphics	base graphics
grid	grid graphics
methods	definition of methods and classes for R objects and programming tools
splines	regression spline functions and classes
stats	statistical functions
stats4	statistical functions using S4 classes
tcltk	functions to interface R with Tcl/Tk graphical user interface elements
tools	tools for package development and administration
utils	R utility functions

Package	Description
boot	resampling and bootstrapping methods
class	classification methods
cluster	clustering methods
foreign	functions for reading data stored in various formats (S3, Stata, SAS, Minitab, SPSS, Epi Info)
KernSmooth	methods for kernel smoothing and density estimation (including bivariate kernels)
lattice	Lattice (Trellis) graphics
MASS	contains many functions, tools and data sets from the libraries of “Modern Applied Statistics with S” by Venables & Ripley
mgcv	generalized additive models
nlme	linear and non-linear mixed-effects models
nnet	neural networks and multinomial log-linear models
rpart	recursive partitioning
spatial	spatial analyses (“kriging”, spatial covariance, ...)
survival	survival analyses

¹⁸<http://cran.r-project.org/src/contrib/PACKAGES.html>

How We Can Install Package?





```
R Console

R version 4.0.4 (2021-02-15) -- "Lost Library Book"
Copyright (C) 2021 The R Foundation for Statistical Computing
Platform: x86_64-w64-mingw32/x64 (64-bit)

R is free software and comes with ABSOLUTELY NO WARRANTY.
You are welcome to redistribute it under certain conditions.
Type 'license()' or 'licence()' for distribution details.

Natural language support but running in an English locale

R is a collaborative project with many contributors.
Type 'contributors()' for more information and
'citation()' on how to cite R or R packages in publications.

Type 'demo()' for some demos, 'help()' for on-line help, or
'help.start()' for an HTML browser interface to help.
Type 'q()' to quit R.

> install.packages()
--- Please select a CRAN mirror for use in this session ---
```

Packages

IsoplotR
IsoplotRgui
ISOpureR
isoreader
IsoriX
IsoSpecR
isoSurv
isotone
isotonic.pen
IsotopeR
isotree
ISOweek
ispd
isqg
ISR3
ISRaD
istacr
iSTATS
isva
ISwR
italy
itan
itcSegment
itemanalysis
iteRates
iterators
iterLap
iterpc
itertools
itertools2
ITGM
ITNr
iTOP
itraxR
ITRLearn
ITRSelect
its.analysis
itsadug

OK

Cancel



Type here to search



META ANALYSIS PACKAGES

➤ `install.packages("haven")`

➤ `install.packages("meta")`

➤ `install.packages("metafor")`

➤ `install.packages("rmeta")`

➤ `install.packages("dmetar")`

WHAT IS META-ANALYSIS?

A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable. It widely accepted as a method of summarizing the results of empirical studies within the behavioral, social and health sciences.

A set of methods to systematically and reproducibly search, sample and (statistically) synthesize evidence from studies.

STEPS OF META ANALYSIS

- Specify Problem
- Search for and Identify Studies
- Enter studies into database
- Select Studies for Review
- Abstract / Code Studies
- Select Effect Size Statistic
- Transform and Weight Effect Sizes
- Assess heterogeneity
- Assess Bias
- Synthesize and Present Results

SELECT EFFECT SIZE STATISTIC

- Comparable, standardized numeric scale for evidence across disparate studies
- Amenable to calculation of standard error
Allows weighting of study's contribution to evidence based on sample size
- Different ES's for different kind of outcomes
- Different statistical methods for same ES

Kinds of Effect Statistics

- **Proportion**

 - Central tendencies

- **Standardized mean difference (d)**

 - Group contrasts of continuous measures

- **Correlation coefficient (r)**

 - Linear associations

- **Odds-ratio**

 - Group contrasts of dichotomous measures

TRANSFORM AND WEIGHT THE EFFECT STATISTIC

➤ Transform

- magnitude and direction of the effect
- same scale for all studies

➤ Weight

- inverse variance gives more ‘weight’ to larger studies
 - sample size is key ("n = "precision)
 - standard error
 - means, correlations, proportions, odds
- not well-suited to complex procedures like multiple logistic regression

Why Weight Effect Sizes?

- Studies vary in size.
- ES based on 100 subjects assumed more “precise” estimate of population ES than ES based on 10 subjects.
- Larger studies *should* carry more “weight”.
- Weighting by the *inverse variance* optimal approach

Fixed Effects vs. Random Effects

Two statistical approaches to calculating the variance for the weighted mean effect statistic.

➤ Fixed Effects

Variance of synthesized effect statistic based only on studies included in the analysis

➤ Random Effects

Variance of synthesized effect statistic based on idea that studies included in the analysis are a random *sample* of all possible studies that could have been included “conservative” vs. “abstruse and uninformative”

Fixed Effects Model

“What is the effect size based solely on the evidence of the studies included in the meta-analysis?”

- Total variance measured only on basis of within-study variance
- Studies weighted on basis of their inverse variance (sample size)
- Approach recommended by Sir Richard Peto and others

Random Effects Model

“What is the average effect size based on the studies included in the meta-analysis *as a sample* of all possible studies?”

- Total variance includes between-study as well as within-study variance
- As between-study variance becomes larger (heterogeneity) dominates, swamps within-study variance and all *studies weighted equally* *collection of separate studies vs. sample from underlying population of studies!*

Fixed Effects vs. Random Effects

When there is little or no heterogeneity, essentially return the same results

Random effects models do not ‘control’ for heterogeneity, rather they are assuming a different underlying model.

Some researchers believe that when there is evidence of heterogeneity, shouldn’t combine studies at all.

Caution if random effects return meaningfully different results from fixed effects

ASSESSING HETEROGENEITY

Test the assumption that all effect sizes are measuring a single, underlying mean.

➤ **Cochran's Q test**

➤ **I² index**

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

ASSESSING BIAS

Some biases are peculiar to meta-analysis.

Positive results are more likely to be!

- Published (publication bias)
- Published quickly (time lag bias)
- Published in English (language bias)
- Published more than once
- Be cited by others (citation bias)

will be present to some extent in all meta analyses. Need to assess *how much* of a problem it is.

PRESENTING RESULTS

➤ Abstract

- Background (include statement of the main research question)
- Methodology/Principal Findings
- Conclusions/Significance

➤ Introduction

➤ Methods

- Searching - describe information sources, restrictions
- Selection - inclusion and exclusion criteria
- Data abstraction
- Validity Assessment
- Study characteristics e.g. type of study designs, participants' characteristics
- Quantitative data synthesis - measures of effect, method of combining results, missing data; how statistical heterogeneity was assessed

➤ Results

- Flow of included studies
- Study characteristics
- Quantitative data synthesis- agreement on the selection and validity assessment, simple summary results, Funnel plots, Forest plots

➤ Discussion

➤ Limitations

EXAMPLE:

IMPORTING DATASET FROM STATA

```
> setwd("S:/_STAFF/Gulser/R NOTES/META ANALYSIS/data")  
> dataset<-read_dta('all832525.dta')  
> attach(dataset)
```

```
> summary(dataset)
```

Author	year	nTreat	meanTreat	sdTreat	nCont	meanCont
Length:9	Min. :2000	Min. : 5.00	Min. :207.0	Min. :24.20	Min. : 7.00	Min. :163.0
Class :character	1st Qu.:2003	1st Qu.: 10.00	1st Qu.:232.0	1st Qu.:30.00	1st Qu.: 18.00	1st Qu.:227.0
Mode :character	Median :2006	Median : 14.00	Median :295.0	Median :60.00	Median : 35.00	Median :230.6
	Mean :2006	Mean : 27.78	Mean :290.5	Mean :54.72	Mean : 40.78	Mean :230.0
	3rd Qu.:2008	3rd Qu.: 32.00	3rd Qu.:351.0	3rd Qu.:67.00	3rd Qu.: 45.00	3rd Qu.:246.0
	Max. :2010	Max. :100.00	Max. :394.0	Max. :93.00	Max. :143.00	Max. :272.0

sdCont
Min. : 13.70
1st Qu.: 23.00
Median : 65.00
Mean : 64.21
3rd Qu.: 94.00
Max. :125.00

```
> m<-metacont(nTreat, meanTreat, sdTreat, nCont, meanCont, sdCont, studlab=paste(Author, year), data=dataset, prediction=TRUE, sm="SMD")
> m
```

	SMD	95%-CI	%W(fixed)	%W(random)
Yamaguchi et al 2000	4.9370 [3.7759; 6.0982]		2.8	10.5
Schibata et al 2003	4.1199 [2.2681; 5.9718]		1.1	7.7
Balzano et al 2003	-0.3068 [-0.8606; 0.2470]		12.4	12.8
Su et al 2004	6.7789 [3.8744; 9.6835]		0.5	4.6
Muller et al 2006	0.4257 [-0.0177; 0.8692]		19.4	13.1
Crippa et al 2007	0.3392 [-0.0148; 0.6933]		30.4	13.4
Ocuin et al 2008	0.9241 [0.1694; 1.6788]		6.7	12.1
Shikano et al 2009	0.5647 [0.0467; 1.0826]		14.2	12.9
Lee et al 2010	0.1838 [-0.3654; 0.7331]		12.6	12.8

Number of studies combined: k = 9

	SMD	95%-CI	z	p-value
Fixed effect model	0.5281 [0.3330; 0.7231]		5.31	< 0.0001
Random effects model	1.4180 [0.6480; 2.1880]		3.61	0.0003
Prediction interval	[-1.2550; 4.0910]			

Quantifying heterogeneity:

tau^2 = 1.1235 [1.1753; 12.5642]; tau = 1.0599 [1.0841; 3.5446]
 I^2 = 92.0% [87.1%; 95.1%]; H = 3.54 [2.78; 4.50]

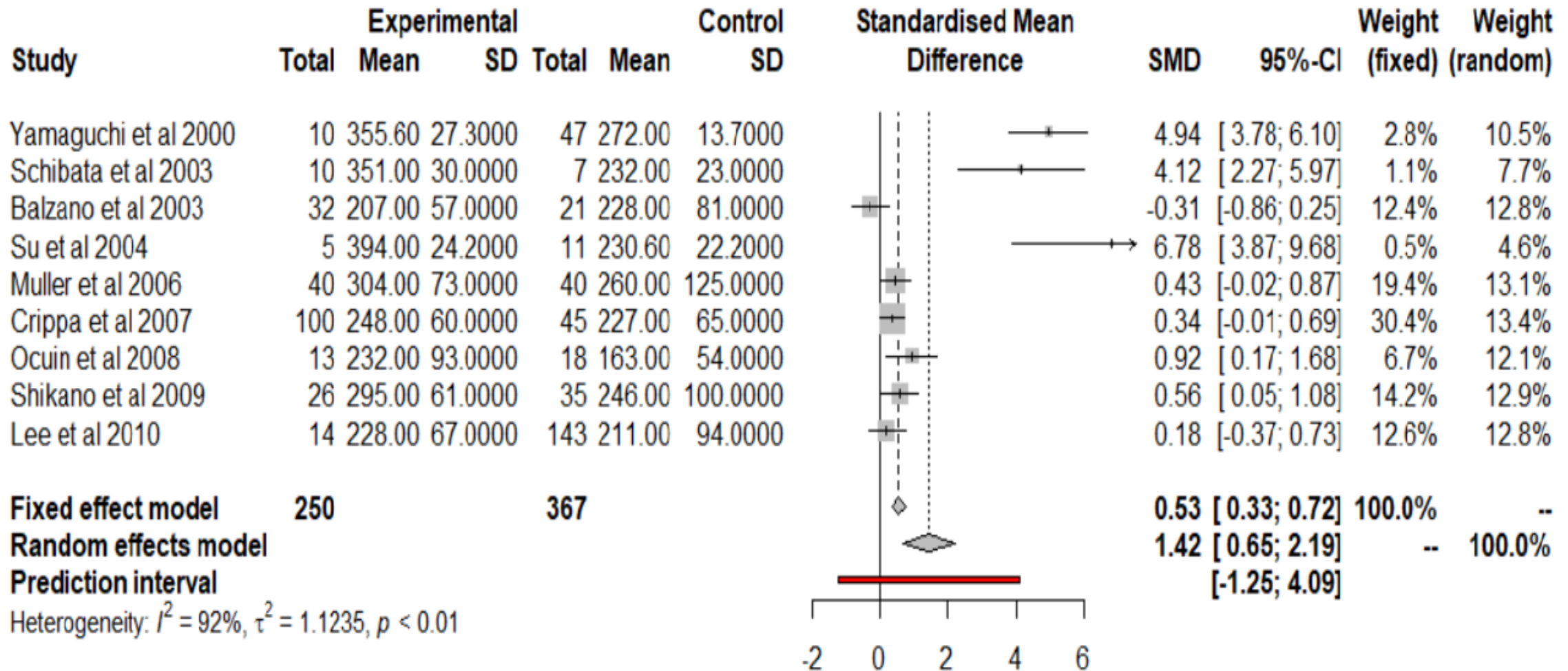
Test of heterogeneity:

Q	d.f.	p-value
100.25	8	< 0.0001

Details on meta-analytical method:

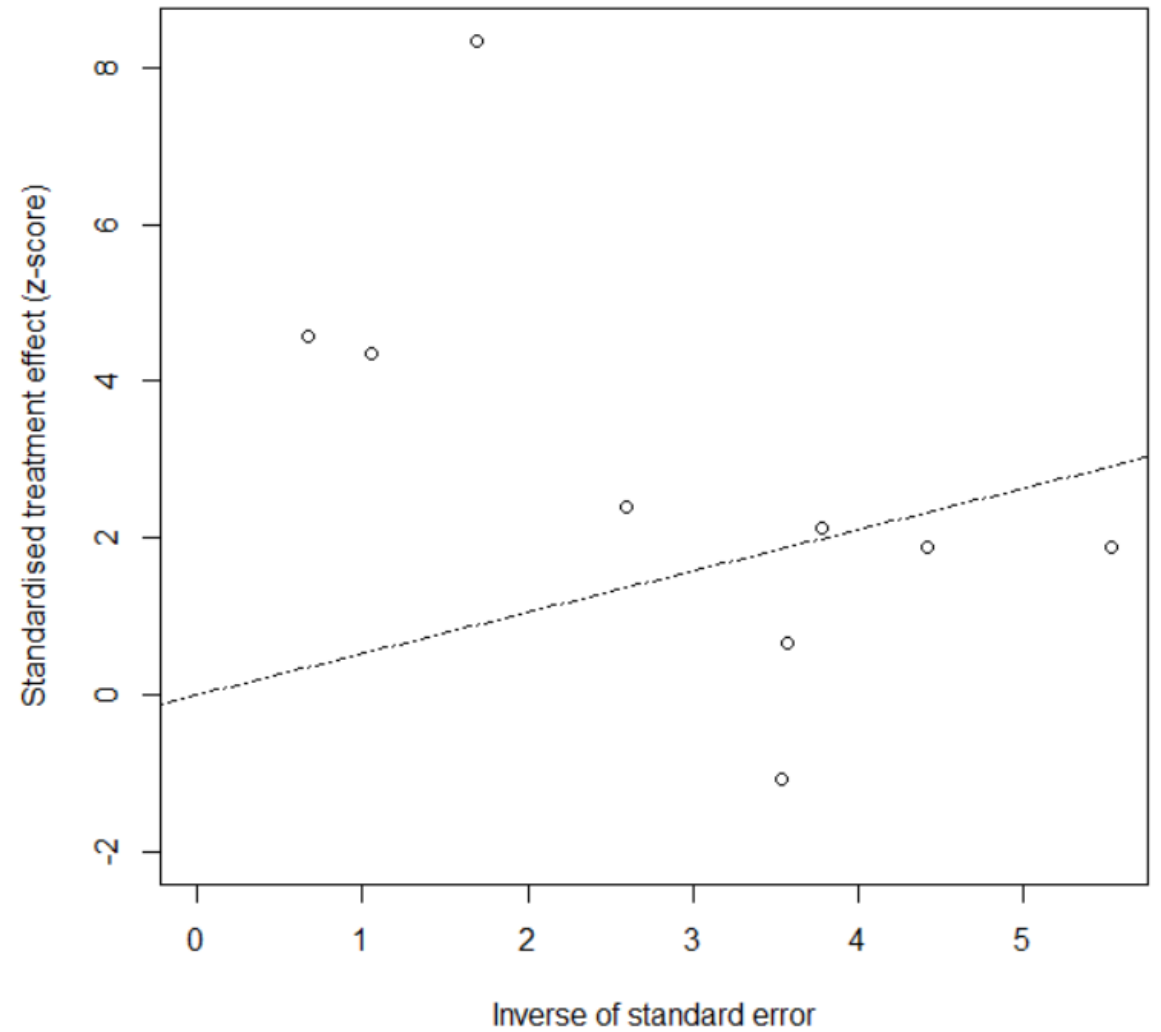
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
- Jackson method for confidence interval of tau^2 and tau
- Hedges' g (bias corrected standardised mean difference)

FOREST PLOT



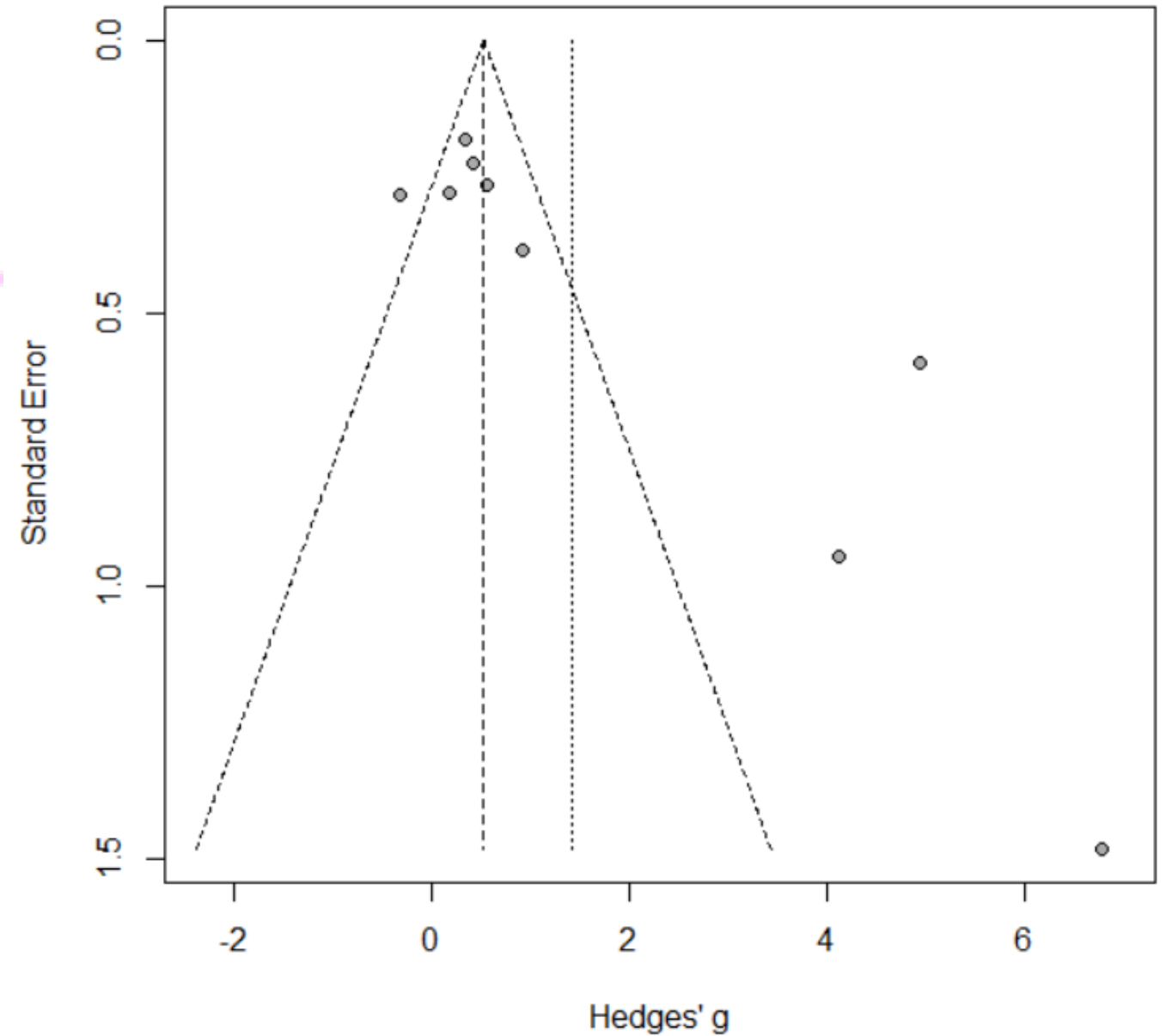
RADIAL PLOT

```
> radial(m)
```



FUNNEL PLOT

```
> funnel(m)  
> funnel(m,xlab = "Hedges' g")
```



```
> metabias(m)
```

```
Warning message:
```

```
Number of studies (k=9) too small to test for small study effects (k.min=10). Change argument 'k.min' if appropriate.
```

```
> metabias(m, k.min=9, method="Egger")  
Linear regression test of funnel plot asymmetry
```

```
Test result: t = 3.58, df = 7, p-value = 0.0090
```

```
Sample estimates:
```

	bias	se.bias	intercept	se.intercept
	5.9217	1.6542	-1.0482	0.4940

```
Details:
```

- multiplicative residual heterogeneity variance ($\tau^2 = 5.0594$)
- predictor: standard error
- weight: inverse variance
- reference: Egger et al. (1997), BMJ

```
> metabias(m, k.min=9, method="Thompson")  
Linear regression test of funnel plot asymmetry
```

```
Test result: t = 6.16, df = 7, p-value = 0.0005
```

```
Sample estimates:
```

	bias	se.bias	intercept	se.intercept
	6.1342	0.9962	-1.1036	0.4338

```
Details:
```

- additive residual heterogeneity variance ($\tau^2 = 0.3703$)
- DerSimonian-Laird estimator for τ^2
- predictor: standard error
- weight: inverse variance
- reference: Thompson & Sharp (1999), Stat Med

```
> trimfill(m)
```

	SMD	95%-CI	%W (random)
Yamaguchi et al 2000	4.9370	[3.7759; 6.0982]	8.7
Schibata et al 2003	4.1199	[2.2681; 5.9718]	7.1
Balzano et al 2003	-0.3068	[-0.8606; 0.2470]	9.7
Su et al 2004	6.7789	[3.8744; 9.6835]	5.0
Muller et al 2006	0.4257	[-0.0177; 0.8692]	9.8
Crippa et al 2007	0.3392	[-0.0148; 0.6933]	9.9
Ocuin et al 2008	0.9241	[0.1694; 1.6788]	9.4
Shikano et al 2009	0.5647	[0.0467; 1.0826]	9.8
Lee et al 2010	0.1838	[-0.3654; 0.7331]	9.7
Filled: Schibata et al 2003	-3.4665	[-5.3184; -1.6147]	7.1
Filled: Yamaguchi et al 2000	-4.2836	[-5.4448; -3.1225]	8.7
Filled: Su et al 2004	-6.1255	[-9.0301; -3.2210]	5.0

Number of studies combined: k = 12 (with 3 added studies)

	SMD	95%-CI	z	p-value
Random effects model	0.3418	[-0.5738; 1.2574]	0.73	0.4644
Prediction interval		[-3.0989; 3.7825]		

Quantifying heterogeneity:

$\tau^2 = 2.1664$ [2.5314; 19.4562]; $\tau = 1.4719$ [1.5911; 4.4109]
 $I^2 = 94.5\%$ [92.0%; 96.2%]; $H = 4.26$ [3.55; 5.13]

Test of heterogeneity:

Q	d.f.	p-value
199.98	11	< 0.0001

Details on meta-analytical method:

- Inverse variance method
- DerSimonian-Laird estimator for τ^2
- Jackson method for confidence interval of τ^2 and τ
- Trim-and-fill method to adjust for funnel plot asymmetry