```
> help.start()
  > exp(-5)
  [1] 0.006738
        9
        > log(3.8
        + )
        [1] 1.335001
```

Virasakdi Chongsuvivatwong

Analysis of epidemiological data using R and Epicalc

Second Edition

Epidemiology Unit
Prince of Songkla University
THAILAND

Analysis of Epidemiological Data Using
R and Epicalc Second Edition

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First Paperback Edition

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Editor : Edward B. McNeil

First published : Chanuang Press
Soi 2, 11 Phetkaem Rd, Hat Yai, Songkhla 90110
Thailand

Book design by : Patcharin Potong
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Hat Yai, Songkhla 90110, Thailand

Cover image : Lisa Schwarb
Graphic designer
Special Programme for Research and Training in
Tropical Diseases (TDR) World Health Organisation

ISBN : 978-616-271-065-0

Printed in Thailand
First Paperback Printing, 2008
2nd Edition Paperback Printing, 2012

R and Epicalc

Preface

Data analysis is very important in epidemiological research. The capacity of computing facilities has been steadily increasing, moving state of the art epidemiological studies along the same direction of computer advancement. Currently, there are many commercial statistical software packages widely used by epidemiologists around the world. For developed countries, the cost of software is not a major problem. For developing countries however, the real cost is often too high. Several researchers in developing countries thus eventually rely on a pirated copy of the software.

Freely available software packages are limited in number and readiness of use. EpiInfo, for example, is free and useful for data entry and simple data analysis. Advanced data analysts however find it too limited in many aspects. For example, it is not suitable for data manipulation for longitudinal studies. Its regression analysis facilities cannot cope with repeated measures and multi-level modelling. The graphing facilities are also limited.

A relatively new and freely available software called **R** is promising. Supported by leading statistical experts worldwide, it has almost everything that an epidemiological data analyst needs. However, it is difficult to learn and to use compared with similar statistical packages for epidemiological data analysis such as Stata. The purpose of this book is therefore to bridge this gap by making **R** easy to learn for researchers from developing countries and also to promote its use.

My experience in epidemiological studies spans over twenty years with a special fondness of teaching data analysis. Inspired by the spirit of the open-source software philosophy, I have spent a tremendous effort exploring the potential and use of **R**. For four years, I have been developing an add-on package for **R** that allows new researchers to use the software with enjoyment. More than twenty chapters of lecture notes and exercises have been prepared with datasets ready for self-study.

Supported by WHO, TDR and the Thailand Research Fund, I have also run a number of workshops for this software in developing countries including Thailand, Myanmar, North Korea, Maldives and Bhutan, where **R** and Epicalc was very much welcomed. With this experience, I hereby propose that the use of this software should be encouraged among epidemiological researchers, especially for those who cannot afford to buy expensive commercial software packages.

R is an environment that can handle several datasets simultaneously. Users get access to variables within each dataset either by copying it to the search path or by including the dataset name as a prefix. The power of **R** in this aspect is a drawback in data manipulation. When creating a variable or modifying an existing one, without prefixing the dataset name, the new variable is isolated from its parental dataset. If prefixing is the choice, the original data is changed but not the copy in the search path. Careful users need to remove the copy in the search path and recopy the new dataset into it. The procedure in this aspect is clumsy. Not being tidy will eventually end up with too many copies in the search path overloading the system or confusing the analyst on where the variable is actually located.

Epicalc presents a concept solution for common types of work where the data analyst works on one dataset at a time using only a few commands. In Epicalc the user can virtually eliminate the necessity of specifying the dataset and can avoid overloading of the search path very effectively and efficiently. In addition to make tidying of memory easy to accomplish, Epicalc makes it easy to recognize the variables by adopting variable labels or descriptions which have been prepared from other software, such as SPSS or Stata, or locally prepared by Epicalc itself.

R has very powerful graphing functions that the user has to spend time learning. Epicalc exploits this power by producing a nice plot of the distribution automatically whenever a single variable is summarised. A breakdown of the first variable by a second categorical variable is also simple and graphical results are automatically displayed. This automatic graphing strategy is also applied to one-way tabulation and two-way tabulation. Description of the variables and the value or category labels are fully exploited with these descriptive graphs.

Additional epidemiological functions added in by Epicalc include calculation of sample size, matched 1:n (n can vary) tabulation, kappa statistics, drawing of ROC curve from a table or from a logistic regression results, population pyramid plots from age and sex and follow-up plots.

R has several advanced regression modelling functions such as multinomial logistic regression, ordinal logistic regression, survival analysis and multi-level modelling. By using Epicalc nice tables of odds ratios and 95% CI are produced, ready for simple transferal into a manuscript document with minimal further modification required.

Although use of Epicalc implies a different way of working with **R** from conventional use, installation of Epicalc has no effect on any existing or new functions of **R**. Epicalc functions only increase efficiency of data analysis and makes **R** easier to use.

This book is essentially about learning **R** with an emphasis on Epicalc. Readers should have some background in basic computer usage. With **R**, Epicalc and the supplied datasets, the users should be able to go through each lesson learning the concepts of data management, related statistical theories and the practice of data analysis and powerful graphing.

The first four chapters introduce **R** concepts and simple handling of important basic elements such as scalars, vectors, matrices, arrays and data frames. Chapter 5 deals with simple data exploration. Date and time variables are defined and dealt with in Chapter 6 and fully exploited in data from a real outbreak investigation in Chapter 7. Descriptive statistics and one-way tabulations are automatically accompanied by corresponding graphs making it rather unlikely that important information is overlooked. Finally, time plots of exposure and disease onsets are plotted with a series of demonstrating commands. Chapter 8 continues to investigate the outbreak by two-way tabulation. Various kinds of risk assessment, such as the risk ratio and protective efficacy, are analysed with numeric and graphic results.

Chapter 9 extends the analysis of the dataset to deal with levels of association or odds ratios. Stratified tabulation, the Mantel-Haenzsel odds ratio, and test of homogeneity of odds ratios are explained in detail. All results are complemented by simultaneous plots. With these graphs, the concept of confounding is made more understandable.

Before proceeding further, the reader has a thorough exercise of data cleaning and standard data manipulation in Chapter 10. Scatter plots, simple linear regression and analysis of variance are presented in Chapter 11. Stratified scatter plots to enhance the concept of confounding and interaction for continuous outcome variables are given in Chapter 12. Curvilinear models are discussed in Chapter 13. Linear modelling is extended to generalized linear modelling in Chapter 14.

For binary outcome variables, Chapter 15 introduces logistic regression with additional comparison with stratified cross-tabulation learned in Chapter 9. The concept of a matched case control study is discussed in Chapter 16 with matched tabulation for 1:1 and 1:n matching. Finally, conditional logistic regression is applied. Chapter 17 introduces polytomous logistic regression using a case-control study in which one type of case series is compared with two types of control groups. Ordinal logistic regression is applied for ordered outcomes in Chapter 18.

For a cohort study, with grouped exposure datasets, Poisson regression is used in Chapter 19. Extra-Poisson regression for overdispersion is also discussed. This includes modeling the outcome using the negative binomial error distribution. Multi-level modelling and longitudinal data analysis are discussed in Chapter 20.

For cohort studies with individual follow-up times, survival analysis is discussed in Chapter 21 and the Cox proportional hazard model is introduced in Chapter 22. In chapter 23 the focus is on analyzing datasets involving attitudes, such as those encountered in the social sciences. Chapter 24 deals with day-to-day work in calculation of sample sizes and the technique of documentation that all professional data analysts must master is explained in Chapter 25.

Some suggested strategies for handling large datasets are given in chapter 26. The book ends with a demonstration of the `tableStack` command, which dramatically shortens the preparation of a tidy stack of tables with a special technique of copy and paste into a manuscript.

At the end of each chapter some references are given for further reading. Most chapters also end with some exercises to practice on. Solutions to these are given at the end of the book.

This edition was written partly as a response to comments from readers of the first edition on certain unclear points a well as to correct typographical errors and partly due to the addition of two chapters related to computation in clinical epidemiology, namely Statistics of Agreement and Diagnostic Tests.

The new chapter on agreement explains the importance of assessment of reproducibility of measurements made by instruments or persons on different occasions and between/among assessors on the same set of study subjects.

The diagnostic test chapter reviews basic concepts and terms of diagnostic tests and shows how its limitations lead to distortion of study results. In computation of the receiver operating characteristic curve, a well known term to most epidemiologists, the chapter demonstrates that area under the curve is not sensitive enough to use for comparing two logistic regression models on the same data set.

Some of the output from Epicalc functions in this edition may be slightly different from the ones shown in the previous edition as some functions have been modified. New functions have also been added since the printing of the first edition. Readers can explore these at the end of the book or from the index of the help pages for the Epicalc package.

Virasakdi Chongsuvivatwong

July, 2012

Colour

It is assumed that the readers of this book will simultaneously practice the commands and see the results on the screen. The explanations in the text sometimes describe the colour of graphs that appear in black and white in this book (the reason for this is purely for reducing the printing costs). The electronic copy of the book, however, does include colour.

Explanations of fonts used in this book

MASS	An R package or library
`Attitudes`	An R dataset
`plot`	An R function
`summ`	An Epicalc function (italic)
'`abc`'	An R object
'pch'	An argument to a function
'saltegg'	A variable within a data frame
"**data.txt**"	A data file on disk

Table of Contents

Chapter 1: Starting to use R

This chapter concerns first use of **R**, covering installation, how to obtain help, syntax of R commands and additional documentation. Note that this book was written for Windows users, however **R** also works on other operating systems.

Installation

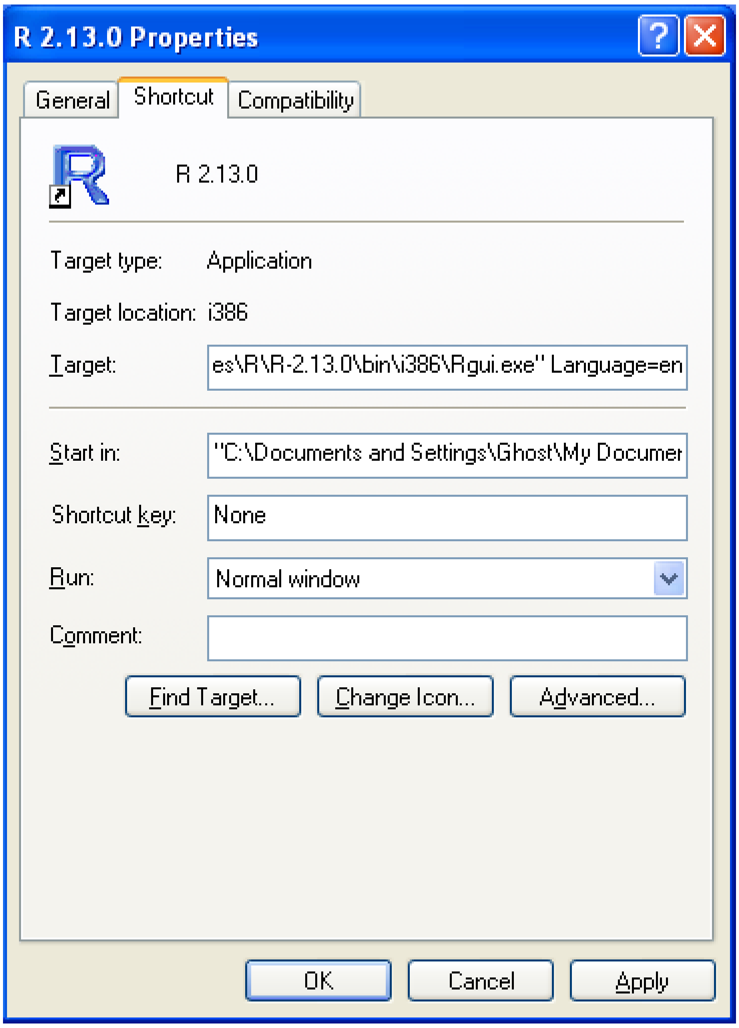
R is distributed under the terms of the GNU General Public License. It is freely available for use and distribution under the terms of this license. The latest version of **R** and Epicalc and their documentation can be downloaded from CRAN (the Comprehensive R Archive Network).

The main web site is http://cran.r-project.org/ but there are mirrors all around the world. Users should download the software from the nearest site. **R** runs on the three common contemporary operating systems, Linux, MacOS X and Windows. To install **R**, first go to the CRAN website and select your operating system from the top of the screen. For Windows users click the Windows link and follow the link to the base subdirectory. In this page you can download the setup file for Windows, which at the time of publication of this book was R-2.13.0-win32.exe. Click this link and click the "Save" button.

The set-up file for **R** is around 30Mb. To run the installation simply double-click this file and follow the instructions. After installation, a shortcut icon of **R** should appear on the desktop. Right-click this **R** icon to change its start-up properties. Replace the default 'Start in' folder with your own working folder. This is the folder where you want **R** to work. You can create multiple shortcut icons with different start-in folders for each project you are working on.

Suppose the work related to this book will be stored in a folder called 'C:\RWorkplace'. The 'Properties' of the icon should have the 'Start in:' text box filled with 'C:\RWorkplace' (do not type the single quote signs ' and '. They are used in this book to indicate objects or technical names).

R detects the main language of the operating system in the computer and tries to use menus and dialog boxes in that language. For example, if you are running **R** on a Windows XP in the Chinese language, the menus and dialog boxes will appear in Chinese. Since this book is written in English, it is advised to set the language to be English so that the responses on your computer will be the same as those in this book. In the 'Shortcut' tab of the **R** icon properties, add `Language=en` at the end of the 'Target'. Include a space before the word 'Language'.



R 2.13.0 Properties

R 2.13.0

Target type: Application

Target location: i386

Target: es\R\R-2.13.0\bin\i386\Rgui.exe" Language=en

Start in: "C:\Documents and Settings\Ghost\My Documen

Shortcut key: None

Run: Normal window

Comment:

So, the Target text box for R-2.13.1 version icon would be:

```
"C:\Program Files\R\R-2.13.0\bin\i386\Rgui.exe" Language=en
```

To use this book efficiently, a specialised text editor such as *Crimson Editor* or *Tinn-R* must be installed on your computer. In addition, the Epicalc package needs to be installed and loaded.

Text Editors

Tinn-R

Tinn-R is probably the best text file editor to use in conjunction with the **R** program. It is specifically designed for working with **R** script files. In addition to syntax highlighting of **R** code, Tinn-R can interact with **R** using specific menus and tool bars. This means that sections of commands can be highlighted and sent to the **R** console (sourced) with a single button click. Tinn-R can be downloaded from the Internet at: www.sciviews.org/Tinn-R.

Starting R Program

After modifying the start-up properties of the **R** icon, double-click the **R** icon on the desktop. The program should then start and the following output is displayed on the **R** console.

```
R version 2.13.0 (2011-04-13)
Copyright (C) 2011 The R Foundation for Statistical Computing
ISBN 3-900051-07-0
Platform: i386-pc-mingw32/i386 (32-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.
>
```

The output shown above was produced from **R** version 2.13.0, released on April 13, 2011. The second paragraph declares and briefly explains the warranty and license. The third paragraph gives information about contributors and how to cite **R** in publications. The fourth paragraph suggests a few commands for first-time users to try.

In this book, **R** commands begin with the ">" sign, similar to what is shown at the **R** console window. You should not type the ">". Just type the commands. Within this document both the **R** commands and output lines will be in `Courier New` font whereas the explanatory text are in Times New Roman. Epicalc commands are shown in *italic*, whereas standard **R** commands are shown in normal font style.

The first thing to practice is to quit the program. Click the cross sign at the far right upper corner of the program window or type the following at the **R** console:

```
> q()
```

A dialog box will appear asking "Save workspace image?" with three choices: "Yes", "No" and "Cancel". Choose "Cancel" to continue working with **R**. If you choose "Yes", two new files will be created in your working folder. Any previous commands that have been typed at the **R** console will be saved into a file called '.Rhistory' while the current workspace will be saved into a file called ".**Rdata**". Notice that these two files have no prefix. In the next session of computing, when **R** is started in this folder, the image of the working environment of the last saved **R** session will be retrieved automatically, together with the command history. Continued use of **R** in this fashion (quitting and saving the unnamed workspace image) will result in these two files becoming larger and larger. Usually one would like to start **R** afresh every time so it is advised to always choose "No" when prompted to save the workspace. Alternatively you may type:

```
> q("no")
```

to quit without saving the workspace image and prevent the dialog box message appearing.

Note that before quitting **R** you can save your workspace image by typing

```
> save.image("C:/RWorkplace/myFile.RData")
```

where '`myFile`' is the name of your file. Then when you quit **R** you should answer "No" to the question.

R libraries & packages

R can be defined as an environment within which many classical and modern statistical techniques, called functions, are implemented. A few of these techniques are built into the base **R** environment, but many are supplied as *packages*. A package is simply a collection of these functions together with datasets and documentation. A *library* is a collection of packages typically contained in a single directory on the computer.

There are about 25 packages supplied with **R** (called “standard” or “recommended” packages) and many more are available through the CRAN web site. Only 7 of these packages are loaded into memory when **R** is executed. To see which packages are currently loaded into memory you can type:

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

The list shown above is in the search path of **R**. When **R** is told to do any work, it will look for a particular object for it to work with from the search path. First, it will look inside '.GlobalEnv', which is the global environment. This will always be the first search position. If **R** cannot find what it wants here, it then looks in the second search position, in this case "package:methods", and so forth. Any function that belongs to one of the loaded packages is always available during an **R** session.

Epicalc package

The Epicalc package can be downloaded from the web site http://cran.r-project.org. On the left pane of this web page, click 'Packages'. Move down along the alphabetical order of various packages to find 'epicalc'. The short and humble description is 'Epidmiological calculator'. Click 'epicalc' to hyperlink to the download page. On this page you can download the Epicalc source code (.tar.gz), and the two binary versions for MacIntosh (.tgz) and Windows (.zip) versions, along with the documentation (.pdf).

The Epicalc package is updated from time to time. The version number is in the suffix. For example, "**epicalc_2.13.0.1.zip**" is the binary file for use on the Windows operating system and the version of Epicalc is 2.13.0.1. A newer version is created to have bugs (errors in the programme) fixed, to improve the features of existing functions and to include new functions.

The file **"epicalc_*version*.zip"** ('version' increases with time) is a compressed file containing the fully compiled Epicalc package for the Windows operating system. Installation of this package must be done within **R** itself. Usually there is only one session of installation needed unless you want to overwrite the old package with a newer one of the same name. You will also need to reinstall this package if you install a new version of **R**. To install Epicalc, click 'Packages' on the menu bar at the top of the window. Choose 'Install packages from local zip files...". When the navigating window appears, browse to find the file and open it.

Successful installation will result in:

```
> utils:::menuInstallLocal()
package 'epicalc' successfully unpacked and MD5 sums checked
updating HTML package descriptions
```

Installation is now complete; however functions within Epicalc are still not available until the following command has been executed:

```
> library(epicalc)
```

Note the use of lowercase letters. When the console accepts the command quietly, we can be reasonably confident that the command has been accepted. Otherwise, errors or warnings will be reported.

A common warning is a report of a conflict. This warning is, most of the time, not very serious. This just means that an object (usually a function) with the same name already exists in the working environment. In this case, **R** will give priority to the object in the earlier order of the search path. The command above must be typed every time a new session of **R** is run.

Updating packages

Whenever a new version of a package is released it is advised to keep up to date by removing (unloading) the old one and loading the new one. To unload the Epicalc package, you may type the following at the **R** console:

```
> detach(package:epicalc)
```

After typing the above command, you may then install the new version of the package as mentioned in the previous section. If there are any problems, you may need to quit **R** and start afresh.

RProfile.site

Whenever **R** is run it will execute the commands in the **"RProfile.site"** file, which is located in the 'C:\Program Files\R\R-2.7.0\etc' folder. Remember to replace the **R** version with the one you have installed. By including the command `library(epicalc)` in the **"RProfile.site"** file, every time **R** is run, the Epicalc package will be automatically loaded and ready for use. You may edit this file and insert the command above.

Your **"RProfile.site"** file should look something like this:

```
library(epicalc)

# Things you might want to change
# options(papersize="a4")
# options(editor="notepad")
# options(pager="internal")
# to prefer Compiled HTML help
# options(chmhelp=TRUE)

# to prefer HTML help
# options(htmlhelp=TRUE)
```

On-line help

On-line help is very useful when using software, especially for first time users. Self-studying is also possible from the on-line help of **R**, although with some difficulty. This is particularly true for non-native speakers of English, where manuals can often be too technical or wordy. It is advised to combine the use of this book as a tutorial and on-line help as a reference manual.

On-line help documentation comes in three different versions in **R**. The default version is to show help information in a separate window within **R**. This format is written in a simple markup language that can be read by **R** and can be converted to LaTeX, which is used to produce the printed manuals. The other versions, which can be set in the "**Rprofile.site**" file mentioned previously, are HTML help (`htmlhelp=TRUE`) and compiled HTML help (`chmhelp=TRUE`). The latter version is Windows specific and if chosen, help documentation will appear in a

Windows help viewer. Each help format has its own advantages and you are free to choose the format you want.

For self study, type

```
> help.start()
```

The system will open your web browser from the main menu of **R**. 'An Introduction to R' is the section that all **R** users should try to read first. Another interesting section is 'Packages'. Click this to see what packages you have available. If the Epicalc package has been loaded properly, then this name should also appear in the list. Click 'Epicalc' to see the list of the functions available. Click each of the functions one by one and you will see the help for that individual function. This information can also be obtained by typing 'help(*myFun*)' at the **R** console, where *'myFun*' is the name of the function. To get help on the 'help' function you can type

```
> help(help)
```

or perhaps more conveniently

```
> ?help
```

For fuzzy searching you can try

```
> help.search("...")
```

Replace the dots with the keyword you want to search for. This function also allows you to search on multiple keywords. You can use this to refine a query when you get too many responses.

Very often the user would want to know how to get other statistical analysis functions that are not available in a currently installed package. A better option would be to search from the CRAN website using the 'search' feature located on the left side of the web page and Google will do a search within CRAN. The results would be quite extensive and useful. The user then can choose the website to go to for further learning.

Now type

```
> search()
```

You should see "package:epicalc" in the list. If the Epicalc package has not been loaded, then the functions contained inside will not be available for use.

Having the Epicalc package in the search path means we can use all commands or functions in that package. Other packages can be called when appropriate. For example, the package **survival** is necessary for survival analysis. We will encounter this in the corresponding section.

The order of the search path is sometimes important. For Epicalc users, it is recommended that any additional library should be called early in the session of **R**, i.e. before reading in and attaching to a data frame. This is to make sure that the active dataset will be in the second search position. More details on this will be discussed in Chapter 4.

Using R

A basic but useful purpose of **R** is to perform simple calculations.

```
> 1+1
[1] 2
```

When you type '1+1' and hit the <Enter> key, **R** will show the result of the calculation, which is equal to 2.

For the square root of 25:

```
> sqrt(25)
[1] 5
```

The wording in front of the left round bracket is called a 'function'. The entity inside the bracket is referred to as the function's 'argument'. Thus in the last example, '`sqrt()`' is a function, and when imposed on 25, the result is 5.

To find the value of *e*:

```
> exp(1)
[1] 2.718282
```

Exponentiation of 1 results in the value of *e*, which is about 2.7. Similarly, the exponential value of -5 or e^{-5} would be

```
> exp(-5)
  [1] 0.006738
```

Syntax of R commands

R will compute only when the commands are syntactically correct. For example, if the number of closed brackets is fewer than the number of opened ones and the <Enter> key is pressed, the new line will start with a '+' sign, indicating that **R** is waiting for completion of the command. After the number of closed brackets equals the number of opened ones, computation is carried out and the result appears.

```
> log(3.8
+ )
[1] 1.335001
```

However, if the number of closed brackets exceeds the number of opened ones, the result is a syntax error, or computer grammatical.

```
> log(3.2))
Error: syntax error
```

R objects

In the above simple calculation, the results are immediately shown on the screen and are not stored. To perform a calculation and store the result in an object type:

```
> a = 3 + 5
```

We can check whether the assignment was successful by typing the name of the newly created object:

```
> a
[1] 8
```

More commonly, the assignment is written in the following way.

```
> a <- 3 + 5
> a
[1] 8
```

For ordinary users, there is no obvious difference between the use of `=` and `<-`. The difference applies at the **R** programming level and will not be discussed here. Although `<-` is slightly more awkward to type than `=`, the former technique is recommended to avoid any confusion with the comparison operator (`==`). Notice that there is no space between the two components of the assignment operator `<-`.

Now create a second object called '`b`' equal to the square root of 36.

```
> b <- sqrt(36)
```

Then, add the two objects together.

```
> a + b
[1] 14
```

We can also compute the value on the left and assign the result to a new object called 'c' on the right, using the *right* assign operator, `->`.

```
> a + 3*b -> c
> c
[1] 26
```

However, the following command does not work.

```
> a + 3b -> c
Error: syntax error
```

R does not recognise '`3b`'. The `*` symbol is needed, which indicates multiplication.

The name of an object can consist of more than one letter.

```
> xyx <- 1
> xyx
[1] 1
```

A nonsense thing can be typed into the **R** console such as:

```
> qwert
Error: Object "qwert" not found
```

What is typed in is syntactically correct. The problem is that '`qwert`' is not a recognizable function nor a defined object.

A dot can also be used as a delimiter for an object name.

```
> baht.per.dollar <- 40
> baht.per.dollar
[1] 40
```

In conclusion, when one types in anything at the **R** console, the program will try to show the value of that object. If the signs `=` or `<-` or `->` are encountered, the value will be stored to the object on the left of `=` and `<-` or the right hand side of `->`.

Character or string objects

Character or string means alphanumeric or letter. Examples include the name of a person or an address. Objects of this type cannot be used for calculation. Telephone numbers and post-codes are also strings.

```
> A <- "Prince of Songkla University"

> A
[1] "Prince of Songkla University"
```

R is case sensitive, so '`A`' is not the same as '`a`'.

```
> a
[1] 8

> A
[1] "Prince of Songkla University"
```

Putting comments in a command line

In this book, as with most other programming documents, the author usually inserts some comments as a part of documentation to remind him/herself or to show some specific issue to the readers.

R ignores any words following the # symbol. Thus, such a sentence can be used for comments. Examples:

```
> 3*3 = 3^2     # This gives a syntax error
> 3*3 == 3^2    # This is correct syntax-wise.
> 3*2 == 3^2    # Correct syntax but the result is FALSE
```

Logical: TRUE and FALSE

In the last few commands:

```
> 3*3 == 3^2
[1] TRUE
```

But

```
> 3*2 == 3^2
[1] FALSE
```

Note that we need two equals signs to check equality but only one for assignment.

```
> 3*2 < 3^2
[1] TRUE
```

Logical connection using & (logical 'and')

Both TRUE and FALSE are logical objects. They are both in upper case. Connection of more than one such object results in either TRUE or FALSE. If all are TRUE, the final result is TRUE. For example:

```
> TRUE & TRUE
[1] TRUE
```

A combination of FALSE with any other logical is always FALSE.

```
> TRUE & FALSE
[1] FALSE

> FALSE & FALSE
[1] FALSE
```

Note that

```
> (FALSE & TRUE) == (TRUE & FALSE)
[1] TRUE
```

Without brackets, computation is carried out from left to right.

```
> FALSE & TRUE == TRUE & FALSE
[1] FALSE
```

Logical connection with | (logical 'or')

This kind of connection looks for anything which is TRUE.

```
> TRUE | TRUE
[1] TRUE

> TRUE | FALSE
[1] TRUE

> 3*3 == 3^2 | 3*2 == 3^2
[1] TRUE
```

Value of TRUE and FALSE

Numerically, TRUE is equal to 1 and FALSE is equal to 0.

```
> TRUE == 1
[1] TRUE

> FALSE == 0
[1] TRUE
```

```
> (3*3 == 3^2) + (9 > 8)
[1] 2
```

Each of the values in the brackets is TRUE, which is equal to 1. The addition of two TRUE objects results in a value of 2. However,

```
> 3*3 == 3^2 + 9 > 8
Error: syntax error in "3*3 == 3^2 + 9 >"
```

This is due to the complicated sequence of the operation. Therefore, it is always better to use brackets in order to specify the exact sequence of computation.

Let's leave **R** for the time being. Answer "Yes" to the question: "Save work space image?".

Please remember that answering "No" is the preferred response in this book as we recommend typing

```
> q("no")
```

to end each **R** session. Responding "Yes" here is just an exercise in understanding the concept of workspace images, which follows in chapter 2.

References

An Introduction to R. ISBN 3-900051-12-7.
R Language Definition. ISBN 3-900051-13-5.

Both references above can be downloaded from the CRAN web site.

Exercises

Problem 1.

The formula for sample size of a descriptive survey is

$$n = \frac{1.96^2}{\delta^2}\pi(1-\pi)$$

where *n* is the sample size,
π is the prevalence in the population (not to be confused with the constant *pi*), and
δ is half the width of the 95% confidence interval (precision).

Compute the required sample size if the prevalence is estimated to be 30% of the population and the 95% confidence interval is not farther from the estimated prevalence by more than 5%.

Problem 2.

Change the above prevalence to 5% and suppose each side of the 95% confidence interval is not farther from the estimated prevalence by more than 2%.

Problem 3.

The term 'logit' denotes 'log{P/(1-P)}' where P is the risk or prevalence of a disease. Compute the logits from the following prevalences: 1%, 10%, 50%, 90% and 100%.

Chapter 2: Vectors

In the previous chapter, we introduced simple calculations and storage of the results of the calculations. In this chapter, we will learn slightly more complicated issues.

History and saved objects

Outside **R**, examine the working folder; you should see two new files: **".Rdata"**, which is the working environment saved from the latest **R** session, and **".Rhistory"**, which recorded all the commands in the preceding **R** session. **".Rdata"** is a binary file and only recognised by the **R** program, while **".Rhistory**" is a text file and can be edited using any text editor such as Notepad, Crimson Editor or Tinn-R.

Open **R** from the desktop icon. You may see this in the last line:

```
[Previously saved workspace restored]
```

This means that **R** has restored commands from the previous **R** session (or history) and the objects stored form this session. Press the up arrow key and you will see the previous commands (both correct and incorrect ones). Press <Enter> following the command; the results will come up as if you continued to work in the previous session.

```
> a
[1] 8

> A
[1] "Prince of Songkla University"
```

Both 'a' and 'A' are retained from the previous session.

Note:
The image saved from the previous session contains only objects in the '.GlobalEnv', which is the first position in the search path. The whole search path is not saved. For example, any libraries manually loaded in the previous session need to be reloaded. However, the Epicalc library is automatically loaded every time we start **R** (from the setting of the "**Rprofile.site**" file that we modified in the previous chapter). Therefore, under this setting, regardless of whether the workspace image has been saved in the previous session or not, Epicalc will always be in the search path.

If you want to remove the objects in the environment and the history, quit **R** without saving. Go to the 'start in' folder and delete the two files **".Rhistory"** and **".Rdata"**. Then restart **R**. There should be no message indicating restoration of previously saved workspace and no history of previous commands.

Concatenation

Objects of the same type, i.e. numeric with numeric, string with string, can be concatenated. In fact, a vector is an object containing concatenated, atomised (no more divisible) objects of the same type.

To concatenate, the function '`c()`' is used with at least one atomised object as its argument. Create a simple vector having the integers 1, 2 and 3 as its elements.

```
> c(1,2,3)
[1] 1 2 3
```

This vector has three elements: 1, 2 and 3. Press the up arrow key to reshow this command and type a right arrow to assign the result to a new object called 'd'. Then have a look at this object.

```
> c(1,2,3) -> d
> d
```

Do some calculation with 'd' and observe the results.

```
> d + 4
> d - 3
> d * 7
> d / 10
> d * d
> d ^ 2
> d / d
> d == d
```

In addition to numbers, words can be used to create string vectors.

```
> B <- c("Faculty of Medicine","Prince of Songkla University")
> B
[1] "Faculty of Medicine"       "Prince of Songkla University"
```

Vectors of systematic numbers

Sometimes a user may want to create a vector of numbers with a certain pattern. The following command will create a vector of integers from 1 to 10.

```
> x <- 1:10; x
 [1]  1  2  3  4  5  6  7  8  9 10
```

For 5 repetitions of 13:

```
> rep(13, times=5)
[1] 13 13 13 13 13
```

The function '`rep`' is used to replicate values of the argument. For sequential numbers from -1 to 11 with an incremental step of 3 type:

```
> seq(from = -1, to = 11, by = 3)
[1] -1  2  5  8 11
```

In this case `seq` is a function with three arguments 'from', 'to' and 'by'. The function can be executed with at least two parameters, 'from' and 'to', since the 'by' parameter has a default value of 1 (or -1 if 'to' is less than 'from').

```
> seq(10, 23)
 [1] 10 11 12 13 14 15 16 17 18 19 20 21 22 23

> seq(10, -3)
 [1] 10  9  8  7  6  5  4  3  2  1  0 -1 -2 -3
```

The order of the arguments 'from', 'to' and 'by' is assumed if the words are omitted. When explicitly given, the order can be changed.

```
> seq(by=-1, to=-3, from=10)
```

This rule of argument order and omission applies to all functions. For more details on `seq` use the help feature.

Subsetting a vector with an index vector

In many instances, only a certain part of a vector needs to be used. Let's assume we have a vector of running numbers from 3 to 100 in steps of 7. What would be the value of the 5th number?

```
> seq(from=3, to=100, by=7) -> x
> x
 [1]  3 10 17 24 31 38 45 52 59 66 73 80 87 94
```

In fact, the vector does not end with 100, but rather 94, since a further step would result in a number that exceeds 100.

```
> x[5]
[1] 31
```

The number inside the square brackets '`[]`' is called a subscript. It denotes the position or selection of the main vector. In this case, the value in the 5th position of the vector 'x' is 31. If the 4th, 6th and 7th positions are required, then type:

```
> x[c(4,6,7)]
[1] 24 38 45
```

Note that in this example, the object within the subscript can be a vector, thus the concatenate function `c` is needed, to comply with the **R** syntax. The following would not be acceptable:

```
> x[4,6,7]
Error in x[4, 6, 7] : incorrect number of dimensions
```

To select '`x`' with the first four elements omitted, type:

```
> x[-(1:4)]
 [1] 31 38 45 52 59 66 73 80 87 94
```

A minus sign in front of the subscript vector denotes removal of the elements of 'x' that correspond to those positions specified by the subscript vector.

Similarly, a string vector can be subscripted.

```
> B[2]
[1] "Prince of Songkla University"
```

Using a subscript vector to select a subset

A vector is a set of numbers or strings. Application of a condition within the subscript results in a subset of the main vector. For example, to choose only even numbers of the vector 'x' type:

```
> x[x/2 == trunc(x/2)]
[1] 10 24 38 52 66 80 94
```

The function `trunc` means to truncate or remove the decimals. The condition that 'x' divided by 2 is equal to its truncated value is true iff (if and only if) 'x' is an even number. The same result can be obtained by using the `subset` function.

```
> subset(x, x/2==trunc(x/2))
```

If only odd numbers are to be chosen, then the comparison operator can simply be changed to `!=`, which means 'not equal'.

```
> subset(x, x/2!=trunc(x/2))
[1]  3 17 31 45 59 73 87
```

Similarly, to choose the elements of 'x' which are greater than 30 type:

```
> x[x>30]
 [1] 31 38 45 52 59 66 73 80 87 94
```

Functions related to manipulation of vectors

R can compute statistics of vectors very easily.

```
> fruits <- c(5, 10, 1, 20)
> summary(fruits)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max. 
    1.0     4.0     7.5     9.0    12.5    20.0 
> sum(fruits)
[1] 36
```

There are 36 fruits in total.

```
> length(fruits)   # number of different types of fruits
[1] 4
> mean(fruits)     # mean of number of fruits
[1] 9
> sd(fruits)       # standard deviation
```

```
[1] 8.205689
> var(fruits)      # variance
[1] 67.33333
```

Non-numeric vectors

Let's create a string vector called '`person`' containing 11 elements.

```
> person <- c("A","B","C","D","E","F","G","H","I","J","K")
```

Alternatively, and more economically:

```
> person <- LETTERS[1:11]
```

Now check the *class* of the '`person`' and '`fruits`' objects.

```
> class(person)
[1] "character"

> class(fruits)
[1] "numeric"
```

Character types are used for storing names of individuals. To store the sex of the person, initially numeric codes are given: 1 for male, 2 for female, say.

```
> sex <- c(1,2,1,1,1,1,1,1,1,1,2)
> class(sex)
[1] "numeric"
> sex1 <- as.factor(sex)   # Creating sex1 from sex
```

The function `as.factor` coerces the object '`sex`' into a *factor*, which is a categorical data type in **R**.

```
> sex1
 [1] 1 2 1 1 1 1 1 1 1 1 2
Levels: 1 2
```

There are two levels of sex.

```
> class(sex1)
[1] "factor"
> is.factor(sex)
[1] FALSE
> is.factor(sex1)
[1] TRUE
```

Now try to label 'sex1'.

```
> levels(sex1) <- c("male", "female")
```

The *levels* of '`sex`' is a string vector used for labeling it.

```
> sex1
 [1] male   female male   male   male   male   male
   [8] male   male   male   female
Levels: male female
```

Ordering elements of a vector

Create an 11-element vector of ages.

```
> age <- c(10,23,48,56,15,25,40,21,60,59,80)
```

To sort the ages:

```
> sort(age)
 [1] 10 15 21 23 25 40 48 56 59 60 80
```

The function `sort` creates a vector with the elements in ascending order. However, the original vector is not changed.

```
> median(age)
[1] 40
```

The median of the ages is 40. To get other quantiles, the function `quantile` can be used.

```
> quantile(age)
  0%  25%  50%  75% 100%
10.0 22.0 40.0 57.5 80.0
```

By default (if other arguments omitted), the 0th, 25th, 50th, 75th and 100th percentiles are displayed. To obtain the 30th percentile of age, type:

```
> quantile(age, prob = .3)
30%
 23
```

Creating a factor from an existing vector

An age group vector can be created from age using the `cut` function.

```
> agegr <- cut(age, breaks=c(0,15,60,100))
```

This creates 3 distinct groups, which we can call 'children', 'adults' and 'elderly'. Note that the minimum and maximum of the arguments in `cut` are the outer most boundaries.

```
> is.factor(agegr)
[1] TRUE
> attributes(agegr)
$levels
[1] "(0,15]"   "(15,60]"  "(60,100]"
$class
[1] "factor"
```

The object '`agegr`' is a factor, with levels shown above. We can check the correspondence of '`age`' and '`agegr`' using the `data.frame` function, which combines (but not saves) the 2 variables in a data frame and displays the result. More details on this function is given the chapter 4.

```
> data.frame(age, agegr)
   age    agegr
```

```
1   10   (0,15]
2   23  (15,60]
3   48  (15,60]
4   56  (15,60]
5   15   (0,15]
6   25  (15,60]
7   40  (15,60]
8   21  (15,60]
9   60  (15,60]
10  59  (15,60]
11  80 (60,100]
```

Note that the 5th person, who is 15 years old, is classified into the first group and the 9th person, who is 60 years old, is in the second group. The label of each group uses a square bracket to end the bin indicating that the last number is included in the group (inclusive cutting). A round bracket in front of the group is exclusive or not including that value. To obtain a frequency table of the age groups, type:

```
> table(agegr)
agegr
  (0,15]  (15,60] (60,100]
       2        8        1
```

There are two children, eight adults and one elderly person.

```
> summary(agegr) # same result as the preceding command
> class(agegr)
[1] "factor"
```

The age group vector is a factor or categorical vector. It can be transformed into a simple numeric vector using the '`unclass`' function, which is explained in more detail in chapter 3.

```
> agegr1 <- unclass(agegr)
> summary(agegr1)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  1.000   2.000   2.000   1.909   2.000   3.000

> class(agegr1)
[1] "integer"
```

Categorical variables, for example sex, race and religion should always be factored. Age group in this example is a factor although it has an ordered pattern. Declaring a vector as a factor is very important, particularly when performing regression analysis, which will be discussed in future chapters.

The unclassed value of a factor is used when the numeric (or integer) values of the factor are required. For example, if we are have a dataset containing a 'sex' variable, classed as a factor, and we want to draw a scatter plot in which the colours of the dots are to be classified by the different levels of 'sex', the colour argument to the plot function would be 'col = unclass(sex)'. This will be demonstrated in future chapters.

Missing values

Missing values usually arise from data not being collected. For example, missing age may be due to a person not giving his or her age. In **R**, missing values are denoted by 'NA', abbreviated from 'Not Available'. Any calculation involving NA will result in NA.

```
> b <- NA
> b * 3
[1] NA

> c <- 3 + b
> c
[1] NA
```

As an example of a missing value of a person in a vector series, type the following commands:

```
> height <- c(100,150,NA,160)
> height
[1] 100 150  NA 160

> weight <- c(33, 45, 60,55)
> weight
[1] 33 45 60 55
```

Among four subjects in this sample, all weights are available but one height is missing.

```
> mean(weight)
[1] 48.25

> mean(height)
[1] NA
```

We can get the mean weight but not the mean height, although the length of this vector is available.

```
> length(height)
[1] 4
```

In order to get the mean of all available elements, the NA elements should be removed.

```
> mean(height, na.rm = TRUE)
[1] 136.6667
```

The argument 'na.rm' means 'not available (value) removed', and is the same as when it is omitted by using the function `na.omit()`.

```
> length(na.omit(height))
[1] 3

> mean(na.omit(height))
[1] 136.6667
```

Thus `na.omit` is an independent function that omits missing values from the argument object. 'na.rm' is an internal argument of descriptive statistics for a vector.

Exercises

Problem 1.

Compute the value of $1^2 + 2^2 + 3^2 ... + 100^2$

Problem 2.

Let '`y`' be a series of integers running from 1 to 1,000. Compute the sum of the elements of '`y`' which are multiples of 7.

Problem 3.

The heights (in cm) and weights (in kg) of 10 family members are shown below:

```
          ht wt
Niece    120 22
Son      172 52
GrandPa  163 71
Daughter 158 51
Yai      153 51
GrandMa  148 60
Aunty    160 50
Uncle    170 67
Mom      155 53
Dad      167 64
```

Create a vector called 'ht' corresponding to the heights of the 11 family members. Assign the names of the family members to the 'names' attribute of this vector.

Create a vector called 'wt' corresponding to the family member's weights.

Compute the body mass index (BMI) of each person where BMI = weight / height^2.

Identify the persons who have the lowest and highest BMI and calculate the standard deviation of the BMI.

Chapter 3: Arrays, Matrices and Tables

Real data for analysis rarely comes as a vector. In most cases, they come as a dataset containing many rows or records and many columns or variables. In **R**, these datasets are called *data frames*. Before delving into data frames, let us go through something simpler such as arrays, matrices and tables. Gaining concepts and skills in handing these types of objects will empower the user to manipulate the data very effectively and efficiently in the future.

Arrays

An array may generally mean something finely arranged. In mathematics and computing, an array consists of values arranged in rows and columns. A dataset is basically an array. Most statistical packages can handle only one dataset or array at a time. **R** has a special ability to handle several arrays and datasets simultaneously. This is because **R** is an object-oriented program. Moreover, **R** interprets rows and columns in a very similar manner.

Folding a vector into an array

Usually a vector has no dimension.

```
> a <- (1:10)
> a
 [1]  1  2  3  4  5  6  7  8  9 10

> dim(a)
NULL
```

Folding a vector to make an array is simple. Just declare or re-dimension the number of rows and columns as follows:

```
> dim(a) <- c(2,5)
> a
     [,1] [,2] [,3] [,4] [,5]
[1,]    1    3    5    7    9
[2,]    2    4    6    8   10
```

The numbers in the square brackets are the row and column subscripts. The command `dim(a) <- c(2,5)` folds the vector into an array consisting of 2 rows and 5 columns.

Extracting cells, columns, rows and subarrays using subscripts

While extracting a subset of a vector requires only one component number (or vector), an array requires two components. Individual elements of an array may be referenced by giving the name of the array followed by two subscripts separated by commas inside the square brackets. The first subscript defines row selection; the second subscript defines column selection. Specific rows and columns may be extracted by omitting one of the components, *but keeping the comma*.

```
> a[1,]     # for the first row and all columns of array 'a'
> a[,3]     # for all rows of the third column
> a[2,4]    # extract 1 cell from the 2nd row and 4th column
> a[2,2:4]  # 2nd row, from 2nd to 4th columns
```

The command `a[,]` and `a[]` both choose all rows and all columns of 'a' and thus are the same as typing 'a'. An array may also have 3 dimensions.

```
> b <- 1:24
> dim(b) <- c(3,4,2)   # or b <- array(1:24, c(3,4,2))

> b
, , 1
     [,1] [,2] [,3] [,4]
[1,]    1    4    7   10
[2,]    2    5    8   11
[3,]    3    6    9   12

, , 2
     [,1] [,2] [,3] [,4]
[1,]   13   16   19   22
[2,]   14   17   20   23
[3,]   15   18   21   24
```

The first value of the dimension refers to the number of rows, followed by number of columns and finally the number of strata.

Elements of this three-dimensional array can be extracted in a similar way.

```
> b[1:3,1:2,2]
     [,1] [,2]
[1,]   13   16
[2,]   14   17
[3,]   15   18
```

In fact, an array can have much higher dimensions, but for most epidemiological analysis are rarely used or needed.

Vector binding

Apart from folding a vector, an array can be created from vector binding, either by column (using the function `cbind)` or by row (using the function `rbind)`. Let's return to our fruits vector.

```
> fruits <- c(5, 10, 1, 20)
```

Suppose a second person buys fruit but in different amounts to the first person.

```
> fruits2 <- c(1, 5, 3, 4)
```

To bind '`fruits`' with '`fruits2`', which are vectors of the same length, type:

```
> Col.fruit <- cbind(fruits, fruits2)
```

We can give names to the rows of this array:

```
> rownames(Col.fruit) <- c("orange","banana","durian","mango")
> Col.fruit
        fruits fruits2
orange       5       1
banana      10       5
durian       1       3
mango       20       4
```

Alternatively, the binding can be done by row.

```
> Row.fruit <- rbind(fruits, fruits2)
> colnames(Col.fruit) <- c("orange","banana","durian","mango")
> Row.fruit
        orange banana durian  mango
fruits       5     10      1     20
fruits2      1      5      3      4
```

Transposition of an array

Array transposition means exchanging rows and columns of the array. In the above example, '`Row.fruits`' is a transposition of '`Col.fruits`' and vice versa. Array transposition is achieved using the `t` function.

```
> t(Col.fruit)
> t(Row.fruit)
```

Basic statistics of an array

The total number of fruits bought by both persons is obtained by typing:

```
> sum(Col.fruit)
```

and the total number of bananas is obtained from:

```
> sum(Col.fruit[2,])
```

To obtain descriptive statistics of each buyer, type:

```
> summary(Col.fruit)
```

And to obtain descriptive statistics of each kind of fruit:

```
> summary(Row.fruit)
```

Now suppose '`fruits3`' is created but with one more kind of fruit added.

```
> fruits3 <- c(20, 15, 3, 5, 8)
> cbind(Col.fruit, fruits3)
        fruits fruits2 fruits3
orange       5       1      20
banana      10       5      15
durian       1       3       3
mango       20       4       5
Warning message:
number of rows of result is not a multiple of vector length
  (arg 2) in: cbind(Col.fruit, fruits3)
```

Note that the last element of '`fruits3`' is removed before being added.

```
> fruits4 <- c(1,2,3)
> cbind(Col.fruit, fruits4)
        fruits fruits2 fruits4
orange       5       1       1
banana      10       5       2
durian       1       3       3
mango       20       4       1
Warning message:
number of rows of result is not a multiple of vector length
  (arg 2) in: cbind(Col.fruit, fruits4)
```

Note that '`fruits4`' is shorter than the length of the first vector argument. In this situation **R** will automatically recycle the element of the shorter vector, inserting the first element of '`fruits4`' into the fourth row, with a warning.

String arrays

Similar to a vector, an array can consist of character string objects.

```
> Thais <- c("Somsri", "Daeng", "Somchai", "Veena")

> dim(Thais) <- c(2,2); Thais
     [,1]     [,2]
[1,] "Somsri" "Somchai"
[2,] "Daeng"  "Veena"
```

Note that the elements are folded in colum-wise, not row-wise, sequence.

Implicit array of two vectors of equal length

Two vectors, especially with the same length, may refer to each other without formal binding.

```
> cities <- c("Bangkok","Hat Yai","Chiang Mai")
> postcode <- c(10000, 90110, 50000)
> postcode[cities=="Bangkok"]
[1] 10000
```

This gives the same result as

```
> subset(postcode, cities=="Bangkok")
[1] 10000
```

For a single vector, thre are many ways to identify the order of a specific element. For example, to find the index of "Hat Yai" in the city vector, the following four commands all give the same result.

```
> (1:length(cities))[cities=="Hat Yai"]
> (1:3)[cities=="Hat Yai"]
> subset(1:3, cities=="Hat Yai")
> which(cities=="Hat Yai")
```

Note that when a character vector is binded with a numeric vector, the numeric vector is coerced into a character vector, since all elements of an array must be of the same type.

```
> cbind(cities,postcode)
     cities       postcode
[1,] "Bangkok"    "10000"
[2,] "Hat Yai"    "90110"
[3,] "Chiang Mai" "50000"
```

Matrices

A matrix is a two-dimensional array. It has several mathematical properties and operations that are used behind statistical computations such as factor analysis, generalized linear modelling and so on.

Users of statistical packages do not need to deal with matrices directly but some of the results of the analyses are in matrix form, both displayed on the screen that can readily be seen and hidden as a *returned object* that can be used later. For exercise purposes, we will examine the covariance matrix, which is an object returned from a regression analysis in a future chapter.

Tables

A table is an array emphasizing the relationship between values among cells. Usually, a table is a result of an analysis, e.g. a cross-tabulation between to categorical variables (using function `table`).

Suppose six patients who are male, female, female, male, female and female attend a clinic. If the code is 1 for male and 2 for female, then to create this in **R** type:

```
> sex <- c(1,2,2,1,2,2)
```

Similarly, if we characterize the ages of the patients as being either young or old and the first three patients are young, the next two are old and the last one is young, and the codes for this age classification are 1 for young and 2 for old, then we can create this in **R** by typing.

```
> age <- c(1,1,1,2,2,1)
```

Suppose also that these patients had one to six visits to the clinic, respectively.

```
> visits <- c(1,2,3,4,5,6)

> table1 <- table(sex, age); table1
   age
sex 1 2
  1 1 1
  2 3 1
```

Note that `table1` gives counts of each combination of the vectors `sex` and `age` while '`table2`' (below) gives the sum of the number of visits based on the four different combinations of `sex` and `age`.

```
> table2 <- tapply(visits, list(Sex=sex, Age=age), FUN=sum)

> table2
   Age
Sex  1 2
  1  1 4
  2 11 5
```

To obtain the mean of each combination type:

```
> tapply(visits, list(Sex=sex, Age=age), FUN=mean)

   Age
Sex     1 2
  1 1.000 4
  2 3.667 5
```

Although '`table1`' has class *table*, the class of '`table2`' is still a *matrix*. One can convert it simply using the function `as.table`.

```
> table2 <- as.table(table2)
```

Summary of table vs summary of array

In **R**, applying the function `summary` to a table performs a chi squared test of independence.

```
> summary(table1)
Number of cases in table: 6
Number of factors: 2
Test for independence of all factors:
        Chisq = 0.375, df = 1, p-value = 0.5403
        Chi-squared approximation may be incorrect
```

In contrast, applying `summary` to a non-table array produces descriptive statistics of each column.

```
> is.table(Col.fruits)
[1] FALSE

> summary(Col.fruits)
       fruits          fruits2    
 Min.   : 1.0   Min.   :1.00  
 1st Qu.: 4.0   1st Qu.:2.50  
 Median : 7.5   Median :3.50  
 Mean   : 9.0   Mean   :3.25  
 3rd Qu.:12.5   3rd Qu.:4.25  
 Max.   :20.0   Max.   :5.00  

> fruits.table <- as.table(Col.fruits)
> summary(fruits.table)
Number of cases in table: 49 
Number of factors: 2 
Test for independence of all factors:
        Chisq = 6.675, df = 3, p-value = 0.08302
        Chi-squared approximation may be incorrect

> fisher.test(fruits.table)
        Fisher's Exact Test for Count Data
data:  fruits.table 
p-value = 0.07728
alternative hypothesis: two.sided
```

Lists

An array forces all cells from different columns and rows to be the same type. If any cell is a character then all cells will be coerced into a character. A list is different. It can be a mixture of different types of objects compounded into one entity. It can be a mixture of vectors, arrays, tables or any object type.

```
> list1 <- list(a=1, b=fruits, c=cities)
> list1
$a
[1] 1

$b
[1]  5 10  1 20

$c
[1] "Bangkok"   "Hat Yai"   "Chiang Mai"
```

Note that the arguments of the function `list` consist of a series of new objects being assigned a value from existing objects or values. When properly displayed, each new name is prefixed with a dollar sign, $.

The creation of a list is not a common task in ordinary data analysis. However, a list is sometimes required in the arguments to some functions.

Removing objects from the computer memory also requires a list as the argument to the function `rm`.

```
> rm(list=c("list1", "fruits"))
```

This is equivalent to

```
> rm(list1); rm(fruits)
```

A list may also be returned from the results of an analysis, but appears under a special *class*.

```
> sample1 <- rnorm(10)
```

This generates a sample of 10 numbers from a normal distribution.

```
> qqnorm(sample1)
```

The `qqnorm` function plots the sample quantiles, or the sorted observed values, against the theoretical quantiles, or the corresponding expected values if the data were perfectly normally distributed. It is used here for the sake of demonstration of the `list` function only.

```
> list2 <- qqnorm(sample1)
```

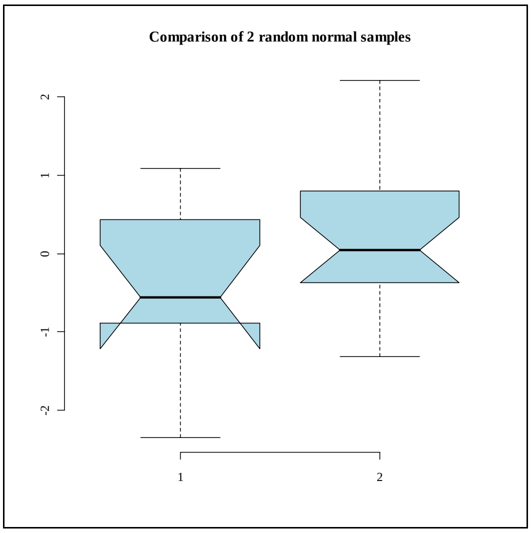
This stores the results into an object called '`list2`'.

```
> list2
$x
 [1]  0.123 -1.547 -0.375  0.655  1.000  0.375 -0.123
 [8] -1.000 -0.655  1.547

$y
 [1] -0.4772 -0.9984 -0.7763  0.0645  0.9595 -0.1103
 [7] -0.5110 -0.9112 -0.8372  2.4158
```

The command `qqnorm(sample1)` is used as a graphical method for checking normality. While it produces a graph on the screen, it also returns a list of the x and y coordinates, which can be saved and used for further calculation.

Similarly, the following command returns another list of objects to facilitate plotting of a boxplot. See the help pages for some interesting examples.

```
> sample2 <- rnorm(20)
> bp <- boxplot(sample1, sample2)
> bp
$stats
          [,1]      [,2]
[1,] -2.34570 -1.308507
[2,] -0.89004 -0.372543
[3,] -0.55554  0.046435
[4,]  0.42912  0.803616
[5,]  1.08444  2.208447

$n
[1] 10 20

$conf
          [,1]     [,2]
[1,] -1.21465 -0.36910
[2,]  0.10356  0.46197

$out
numeric(0)

$group
numeric(0)

$names
[1] "1" "2"

> bxp(bp, notch=TRUE, boxfill="lightblue", frame=FALSE,
  outl=FALSE, main="Comparison of 2 random normal samples")
```



Exercises

Problem 1.

Demonstrate a few simple ways to create the array below

```
     [,1][,2][,3][,4][,5][,6][,7][,8][,9][,10]
[1,]    1   2   3   4   5   6   7   8   9   10
[2,]   11  12  13  14  15   16  7  18  19   20
```

Problem 2.

Extract from the above array the odd numbered columns.

Problem 3.

Cross-tabulation between status of a disease and a putative exposure have the following results:

	Diseased	***Non-diseased***
Exposed	15	20
Non-exposed	30	22

Create the table in **R** and perform chi-squared and Fisher's exact tests.

Chapter 4: Data Frames

In the preceding chapter, examples were given on arrays and lists. In this chapter, data frames will be the main focus. For most researchers, these are sometimes called *datasets*. However, a complete dataset can contain more than one data frame. These contain the real data that most researchers have to work with.

Comparison of arrays and data frames

Many rules used for arrays are also applicable to data frames. For example, the main structure of a data frame consists of columns (or variables) and rows (or records). Rules for subscripting, column or row binding and selection of a subset in arrays are directly applicable to data frames.

Data frames are however slightly more complicated than arrays. All columns in an array are forced to be character if just one cell is a character. A data frame, on the other hand, can have different classes of columns. For example, a data frame can consist of a column of 'idnumber', which is numeric and a column of 'name', which is character.

A data frame can also have extra attributes. For example, each variable can have lengthy variable descriptions. A factor in a data frame often has 'levels' or value labels. These attributes can be transferred from the original dataset in other formats such as Stata or SPSS. They can also be created in **R** during the analysis.

Obtaining a data frame from a text file

Data from various sources can be entered using many different software programs. They can be transferred from one format to another through the ASCII file format. In Windows, a text file is the most common ASCII file, usually having a ".txt" extension. There are several other files in ASCII format, including the "**.R**" command file discussed in chapter 25.

Data from most software programs can be exported or saved as an ASCII file. From Excel, a very commonly used spreadsheet program, the data can be saved as ".csv" (comma separated values) format. This is an easy way to interface between Excel spreadsheet files and **R**. Simply open the Excel file and 'save as' the csv format.

As an example suppose the file **"csv1.xls"** is originally an Excel spreadsheet. After 'save as' into csv format, the output file is called "**csv1.csv**", the contents of which is:

```
"name","sex","age"
"A","F",20
"B","M",30
"C","F",40
```

Note that the characters are enclosed in quotes and the delimiters (variable separators) are commas. Sometimes the file may not contain quotes, as in the file "**csv2.csv**".

```
name,sex,age
A,F,20
B,M,30
C,F,40
```

For both files, the **R** command to read in the dataset is the same.

```
> a <- read.csv("csv1.csv", as.is=TRUE)
> a
  name sex age
1    A   F  20
2    B   M  30
3    C   F  40
```

The argument 'as.is' is set to TRUE to keep all variables as they are. Had this not been specified, the characters would have been coerced into factors. The variable 'name' should not be factored but 'sex' should. The following command should therefore be typed:

```
> a$sex <- factor(a$sex)
```

Note firstly that the object '`a`' has class data frame and secondly that the names of the variables within the data frame '`a`' must be referenced using the dollar sign notation. If not, **R** will inform you that the object '`sex`' cannot be found.

```
> class(a)   # "data.frame"
```

For files with white space (spaces and tabs) as the separator, such as in the file "**data1.txt**", the command to use is `read.table`.

```
> a <- read.table("data1.txt", header=TRUE, as.is=TRUE)
```

The file "**data2.txt**" is in fixed field format without field separators.

```
namesexage
1AF20
2BM30
3CF40
```

To read in such a file, the function `read.fwf` is preferred. The first line, which is the header, must be skipped. The width of each variable and the column names must be specified by the user.

```
> a <- read.fwf("data2.txt", skip=1, width=c(1,1,2), col.names
  = c("name", "sex", "age"), as.is=TRUE)
```

Data entry and analysis

The above section deals with creating data frames by reading in data created from programs outside **R**, such as Excel. It is also possible to enter data directly into **R** by using the function `data.entry`. However, if the data size is large (say more than 10 columns and/or more than 30 rows), the chance of human error is high with the spreadsheet or text mode data entry. A software program specially designed for data entry, such as Epidata, is more appropriate. Their web site is: http://www.epidata.dk. Epidata has facilities for setting up useful constraints such as range checks, automatic jumps and labelling of variables and values (codes) for each variable. There is a direct transfer between Epidata and **R** (using 'read.epiinfo') but it is recommended to export data from Epidata (using the export procedure inside that software) to Stata format and use the function `read.dta` to read the dataset into **R**. Exporting data into Stata format maintains many of the attributes of the variables, such as the variable labels and descriptions.

Clearing memory and reading in data

At the **R** console type:

```
> rm(list=ls())
```

The function `rm` stands for "remove". The command above removes all objects in the workspace. To see what objects are currently in the workspace type:

```
> ls()
character(0)
```

The command `ls()` shows a list of objects in the current workspace. The name(s) of objects have class character. The result "`character(0)`" means that there are no ordinary objects in the environment.

If you do not see "`character(0)`" in the output but something else, it means those objects were left over from the previous **R** session. This will happen if you agreed to save the workspace image before quitting **R**. To avoid this, quit **R** and delete the file "**.Rdata**", which is located in your working folder, or rename it if you would like to keep the workspace from the previous **R** session.

Alternatively, to remove all objects in the current workspace without quitting **R**, type:

```
> zap()
```

This command will delete all ordinary objects from **R** memory. Ordinary objects include data frames, vectors, arrays, etc. Function objects are spared deletion.

Datasets included in Epicalc

Most add-on packages for **R** contain datasets used for demonstration and teaching. To check what datasets are available in all loaded packages in **R** type:

```
> data()
```

You will see names and descriptions of several datasets in various packages, such as **datasets** and **epicalc**. In this book, most of the examples use datasets from the Epicalc package.

Reading in data

Let's try to load an Epicalc dataset.

```
> data(Familydata)
```

The command `data` loads the **`Familydata`** dataset into the **R** workspace. If there is no error you should be able to see this object in the workspace.

```
> ls()
[1] "Familydata"
```

Viewing contents of a data frame

If the data frame is small such as this one (11 records, 6 variables), just type its name to view the entire dataset.

```
> Familydata
   code age  ht wt money sex
1     K   6 120 22     5   F
2     J  16 172 52    50   M
3     A  80 163 71   100   M
4     I  18 158 51   200   F
5     C  69 153 51   300   F
6     B  72 148 60   500   F
7     G  46 160 50   500   F
8     H  42 163 55   600   F
9     D  58 170 67  2000   M
10    F  47 155 53  2000   F
11    E  49 167 64  5000   M
```

To get the names of the variables (in order) of the data frame, you can type:

```
> names(Familydata)
[1] "code"  "age"   "ht"    "wt"    "money" "sex"
```

Another convenient function that can be used to explore the data structure is `str`.

```
> str(Familydata)
'data.frame':   11 obs. of  6 variables:
 $ code : chr  "K" "J" "A" "I" ...
 $ age  : int  6 16 80 18 69 72 46 42 58 47 ...
 $ ht   : int  120 172 163 158 153 148 160 163 170 155 ...
 $ wt   : int  22 52 71 51 51 60 50 55 67 53 ...
 $ money: int  5 50 100 200 300 500 500 600 2000 2000 ...
 $ sex  : Factor w/ 2 levels "F","M": 1 2 2 1 1 1 1 1 2  ...
=============+=== remaining output omitted =====+===========
```

Summary statistics of a data frame

A quick exploration of a dataset should be to obtain the summary statistics of all variables. This can be achieved in a single command.

```
> summary(Familydata)
     code                age             ht       
 Length:11          Min.   : 6.0   Min.   :120  
 Class :character   1st Qu.:30.0   1st Qu.:154  
 Mode  :character   Median :47.0   Median :160  
                    Mean   :45.7   Mean   :157  
                    3rd Qu.:63.5   3rd Qu.:165  
                    Max.   :80.0   Max.   :172  
       wt           money      sex  
 Min.   :22.0   Min.   :   5   F:7  
 1st Qu.:51.0   1st Qu.: 150   M:4  
 Median :53.0   Median : 500        
 Mean   :54.2   Mean   :1023        
 3rd Qu.:62.0   3rd Qu.:1300        
 Max.   :71.0   Max.   :5000        
```

The function `summary` is from the **base** library. It gives summary statistics of each variable. For a continuous variable such as 'age', 'wt', 'ht' and 'money', non-parametric descriptive statistics such as minimum, first quartile, median, third quartile and maximum, as well as the mean (parametric) are shown. There is no information on the standard deviation or the number of observations. For categorical variables, such as 'sex', a frequency tabulation is displayed. The first variable 'code' is a character variable. There is therefore no summary for it.

Compare this result with the version of summary statistics using the function *`summ`* from the Epicalc package.

```
> summ(Familydata)
Anthropometric and financial data of a hypothetical family
No. of observations = 11
  Var. name Obs.  mean    median s.d.    min.   max.
1 code
2 age       11    45.73   47     24.11   6      80
3 ht        11    157.18  160    14.3    120    172
4 wt        11    54.18   53     12.87   22     71
5 money     11    1023.18 500    1499.55 5      5000
6 sex       11    1.364   1      0.505   1      2
```

The function *`summ`* gives a more concise output, showing one variable per line. The number of observations and standard deviations are included in the report replacing the first and third quartile values in the original `summary` function from the **base** library. Descriptive statistics for factor variables use their unclassed values. The values 'F' and 'M' for the variable 'sex' have been replaced by the codes 1 and 2, respectively. This is because **R** interprets factor variables in terms of levels, where each level is stored as an integer starting from 1 for the first level of the factor. Unclassing a factor variable converts the categories or levels into integers. More discussion about factors will appear later.

From the output above the same statistic from different variables are lined up into the same column. Information on each variable is completed without any missing as the number of observations are all 11. The minimum and maximum are shown close to each other enabling the range of the variable to be easily determined.

In addition, summary statistics for each variable is possible with both choices of functions. The results are similar to summary statistics of the whole dataset. Try the following commands:

```
> summary(Familydata$age)
> summ(Familydata$age)
> summary(Familydata$sex)
> summ(Familydata$sex)
```

Note that *`summ`*, when applied to a variable, automatically gives a graphical output. This will be examined in more detail in subsequent chapters.

Extracting subsets from a data frame

A data frame has a subscripting system similar to that of an array. To choose only the third column of **`Familydata`** type:

```
> Familydata[,3]
 [1] 120 172 163 158 153 148 160 163 170 155 167
```

This is the same as

```
> Familydata$ht
```

Note that subscripting the data frame **`Familydata`** with a dollar sign $ and the variable name will extract only that variable. This is because a data frame is also a kind of list (see the previous chapter).

```
> typeof(Familydata)
[1] "list"
```

To extract more than one variable, we can use either the index number of the variable or the name. For example, if we want to display only the first 3 records of 'ht', 'wt' and 'sex', then we can type:

```
> Familydata[1:3,c(3,4,6)]
   ht wt sex
1 120 22   F
2 172 52   M
3 163 71   M
```

We could also type:

```
> Familydata[1:3,c("ht","wt","sex")]

   ht wt sex
1 120 22   F
2 172 52   M
3 163 71   M
```

The condition in the subscript can be a selection criteria, such as selecting the females.

```
> Familydata[Familydata$sex=="F",]
   code age  ht wt money sex
1      K   6 120 22     5   F
4      I  18 158 51   200   F
5      C  69 153 51   300   F
6      B  72 148 60   500   F
7      G  46 160 50   500   F
8      H  42 163 55   600   F
10     F  47 155 53  2000   F
```

Note that the conditional expression must be followed by a comma to indicate selection of all columns. In addition, two equals signs are needed in the conditional expression. Recall that one equals sign represents assignment.

Another method of selection is to use the `subset` function.

```
> subset(Familydata, sex=="F")
```

To select only the 'ht' and 'wt' variables among the females:

```
> subset(Familydata, sex=="F", select = c(ht,wt))
```

Note that the commands to select a subset do not have any permanent effect on the data frame. The user must save this into a new object if further use is needed.

Adding a variable to a data frame

Often it is necessary to create a new variable and append it to the existing data frame. For example, we may want to create a new variable called 'log10money' which is equal to log base 10 of the pocket money.

```
> Familydata$log10money <- log10(Familydata$money)
```

Alternatively we can use the `transform` function.

```
> Familydata <- transform(Familydata, log10money=log10(money))
```

The data frame is now changed with a new variable 'log10money' added. This can be checked by the following commands.

```
> names(Familydata)
> summ(Familydata)

Anthropometric and financial data of a hypothetic family
No. of observations = 11

  Var. name  Obs.  mean    median  s.d.    min.  max.
1 code
2 age        11    45.73   47      24.11   6     80
3 ht         11    157.18  160     14.3    120   172
4 wt         11    54.18   53      12.87   22    71
5 money      11    1023.18 500     1499.55 5     5000
6 sex        11    1.364   1       0.505   1     2
7 log10money 11    2.51    2.7     0.84    0.7   3.7
```

Removing a variable from a data frame

Conversely, if we want to exclude a variable from a data frame, just specify a minus sign in front of the column subscript:

```
> Familydata[,-7]
   code age  ht wt money sex
1     K   6 120 22     5   F
2     J  16 172 52    50   M
3     A  80 163 71   100   M
4     I  18 158 51   200   F
5     C  69 153 51   300   F
6     B  72 148 60   500   F
7     G  46 160 50   500   F
8     H  42 163 55   600   F
9     D  58 170 67  2000   M
10    F  47 155 53  2000   F
11    E  49 167 64  5000   M
```

Note again that this only displays the desired subset and has no permanent effect on the data frame. The following command permanently removes the variable and returns the data frame back to its original state.

```
> Familydata$log10money <- NULL
```

Assigning a NULL value to a variable in the data frame is equivalent to removing that variable.

At this stage, it is possible that you may have made some typing mistakes. Some of them may be serious enough to make the data frame **`Familydata`** distorted or even not available from the environment. You can always refresh the **R** environment by removing all objects and then read in the dataset afresh.

```
> zap()
> data(Familydata)
```

Attaching the data frame to the search path

Accessing a variable in the data frame by prefixing the variable with the name of the data frame is tidy but often clumsy, especially if the data frame and variable names are lengthy. Placing or *attaching* the data frame into the search path eliminates the tedious requirement of prefixing the name of the variable with the data frame. To check the search path type:

```
> search()
 [1] ".GlobalEnv"        "package:epicalc"
 [3] "package:methods"   "package:stats"
 [5] "package:graphics"  "package:grDevices"
 [7] "package:utils"     "package:datasets"
 [9] "package:foreign"   "Autoloads"
[11] "package:base"
```

The general explanation of `search()` is given in Chapter 1. Our data frame is not in the search path. If we try to use a variable in a data frame that is not in the search path, an error will occur.

```
> summary(age)
Error in summary(age) : Object "age" not found
```

Try the following command:

```
> attach(Familydata)
```

The search path now contains the data frame in the second position.

```
> search()
 [1] ".GlobalEnv"        "Familydata"        "package:methods"
 [4] "package:datasets" "package:epicalc"   "package:survival"
 [7] "package:splines"   "package:graphics" "package:grDevices"
[10] "package:utils"     "package:foreign"   "package:stats"
[13] "Autoloads"         "package:base"
```

Since 'age' is inside **Familydata**, which is now in the search path, computation of statistics on 'age' is now possible.

```
> summary(age)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
   6.00   30.00   47.00   45.73   63.50   80.00
```

Attaching a data frame to the search path is similar to loading a package using the `library` function. The attached data frame, as well as the loaded packages, are actually read into **R**'s memory and are resident in memory until they are *detached*. This is true even if the original data frame has been removed from the memory.

```
> rm(Familydata)
> search()
```

The data frame **Familydata** is still in the search path allowing any variable within the data frame to be used.

```
> age
 [1]  6 16 80 18 69 72 46 42 58 47 49
```

Loading the same library over and over again has no effect on the search path but re-attaching the same data frame is possible and may eventually overload the system resources.

```
> data(Familydata)
> attach(Familydata)

      The following object (s) are masked from Familydata
  ( position 3 ) :
         age code ht money sex wt
```

These variables are already in the second position of the search path. Attaching again creates conflicts in variable names.

```
> search()
 [1] ".GlobalEnv"        "Familydata"       "Familydata"
 [4] "package:methods"   "package:datasets" "package:epicalc"
 [7] "package:survival"  "package:splines"  "package:graphics"
[10] "package:grDevices" "package:utils"    "package:foreign"
[13] "package:stats"     "Autoloads"        "package:base"
```

The search path now contains two objects named **Familydata** in positions 2 and 3. Both have more or less the same set of variables with the same names. Recall that every time a command is typed in and the <Enter> key is pressed, the system will first check whether it is an object in the global environment. If not, **R** checks whether it is a component of the remaining search path, that is, a variable in an attached data frame or a function in any of the loaded packages.

Repeatedly loading the same library does not add to the search path because **R** knows that the contents in the library do not change during the same session. However, a data frame can change at any time during a single session, as seen in the previous section where the variable 'log10money' was added and later removed. The data frame attached at position 2 may well be different to the object of the same name in another search position. Confusion arises if an independent object (e.g. vector) is created outside the data frame (in the global environment) with the same name as the data frame or if two different data frames in the search path each contain a variable with the same name. The consequences can be disastrous.

In addition, all elements in the search path occupy system memory. The data frame **`Familydata`** in the search path occupies the same amount of memory as the one in the current workspace. Doubling of memory is not a serious problem if the data frame is small. However, repeatedly attaching to a large data frame may cause **R** to not execute due to insufficient memory.

With these reasons, it is a good practice firstly, to remove a data frame from the search path once it is not needed anymore. Secondly, remove any objects from the environment using `rm(list=ls())` when they are not wanted anymore. Thirdly, do not define a new object (say vector or matrix) that may have the same name as the data frame in the search path. For example, we should not create a new vector called **`Familydata`** as we already have the data frame **`Familydata`** in the search path.

Detach both versions of **`Familydata`** from the search path.

```
> detach(Familydata)
> detach(Familydata)
```

Note that the command *`detachAllData`*`()` in Epicalc removes all attachments to data frames. The command *`zap`*`()` does the same, but in addition removes all non-function objects. In other words, the command *`zap`*`()` is equivalent to `rm(list=`*`lsNoFunction`*`())` followed by *`detachAllData`*`()`.

The 'use' command in Epicalc

Attaching to and detaching from a data frame is often tedious and cumbersome and if there is more than one data frame in the workspace then users must be careful that they are attached to the correct data frame when working with their data. Most data analysis deals only with a single data frame. In order to reduce these steps of attaching and detaching, Epicalc contains a command called *`use`* which eases the process. At the **R** console type:

```
> zap()
> data(Familydata)
> use(Familydata)
```

The command *use*()reads in a data file from Dbase (.dbf), Stata (.dta), SPSS (.sav), EpiInfo (.rec) and comma separated value (.csv) formats, as well as those that come pre-supplied with **R** packages. The **Familydata** data frame comes with *Epicalc*. If you want to read a dataset from a Stata file format, such as "**family.dta**", simply type `use("family.dta")` without typing the `data` command above. The dataset is copied into memory in a default data frame called **.data**. If **.data** already exists, it will be overwritten by the new data frame. The original **Familydata**, however, remains.

In fact, all the datasets in Epicalc were originally in one of the file formats of .dta, .rec, .csv or .txt. These datasets in their original format can be downloaded from http://medipe.psu.ac.th/Epicalc/. If you download the files and set the working directory for **R** to the default folder "C:\RWorkplace", you do not need to type `data(Familydata)` and `use(Familydata)`, but instead simply type:

```
> use("family.dta")
```

The original Stata file will be read into **R** and saved as **.data**. If successful, it will make no difference whether you type `data(Familydata)` followed by `use(Familydata)` or simply `use("family.dta")`.

In most parts of the book, we chose to tell you to type `data(Familydata)` and `use(Familydata)` instead of `use("family.dta")` because the dataset is already in the Epicalc package, which is readily available when you practice Epicalc to this point. However, putting "filename.extension" as the argument such as `use("family.dta")` in this chapter or `use("timing.dta")` in the next chapter, and so forth, may give you a real sense of reading actual files instead of the approach that is used in this book.

The command *use* also automatically places the data frame, **.data**, into the search path. Type:

```
> search()
```

You will see that **.data** is in the second position of the search path. Type:

```
> ls()
```

You will see only the **Familydata** object, and not **.data** because the name of this object starts with a dot and is classified as a hidden object. In order to show that **.data** is really in the memory, Type

```
> ls(all=TRUE)
```

You will see **.data** in the first position of the list.

.data is resistant to zap()

Type the following at the **R** console:

```
> zap()
> ls(all=TRUE)
```

The object **`Familydata`** is gone but **`.data`** is still there. However, the attachment to the search path is now lost

```
> search()
```

In order to put it back to the search path, we have to attach to it manually.

```
> attach(.data)
```

The advantage of *`use`*`()` is not only that it saves time by making `attach` and `detach` unnecessary, but **`.data`** is placed in the search path as well as being made the default data frame. Thus *`des`*`()` is the same as *`des`*`(.data)`, *`summ`*`()` is equivalent to *`summ`*`(.data)`.

```
> des()
> summ()
```

The sequence of commands *`zap`*, `data(datafile)`, *`use`*`(`*`datafile`*`)`, *`des`*`()` and *`summ`*`()` is recommended for starting an analysis of almost all datasets in this book. A number of other commands from the Epicalc package work based on this strategy of making **`.data`** the default data frame and exclusively attached to the search path (all other data frames will be detached, unless the argument '*`clear=FALSE`*' is specified in the *`use`* function). For straightforward data analysis, the command *`use`*`()` is sufficient to create this setting. In many cases where the data that is read in needs to be modified, it is advised to rename or copy the final data frame to **`.data`**. Then detach from the old **`.data`** and re-attach to the most updated one in the search path.

This strategy does not have any effect on the standard functions of **R**. The users of Epicalc can still use the other commands of **R** while still enjoying the benefit of Epicalc.

Exercises

With several datasets provided with *Epicalc*, use the last commands (*`zap`*, `data`, *`use`*, *`des`*, *`summ`*) to have a quick look at them.

Chapter 5: Simple Data Exploration

Data exploration using Epicalc

In the preceding chapter, we learnt the commands *zap* for clearing the workspace and memory, *use* for reading in a data file and *codebook*, *des* and *summ* for initially exploring the data frame, keeping in mind that these are all Epicalc commands. The *use* function places the data frame into a hidden object called **.data**, which is automatically attached to the search path. In this chapter, we will work with more examples of data frames as well as ways to explore individual variables.

```
> zap()
> data(Familydata)
> use(Familydata)
> des()

Anthropometric and financial data of a hypothetical family

No. of observations = 11
  Variable      Class           Description
1 code          character
2 age           integer         Age(yr)
3 ht            integer         Ht(cm.)
4 wt            integer         Wt(kg.)
5 money         integer         Pocket money(B.)
6 sex           factor
```

The first line after the *des*() command shows the data *label*, which is the descriptive text for the data frame. This is usually created by the software that was used to enter the data, such as Epidata or Stata. Subsequent lines show variable names and individual variable descriptions. The variable 'code' is a character string while 'sex' is a factor. The other variables have class integer. A character variable is not used for statistical calculations but simply for labelling purposes or for record identification. Recall that a factor is what **R** calls a categorical or group variable. The remaining integer variables ('age', 'ht', 'wt' and 'money') are intuitively continuous variables. The variables 'code' and 'sex' have no variable descriptions due to omission during the preparation of the data prior to data entry.

```
> summm()

Anthropometric and financial data of a hypothetical family

No. of observations  = 11

  Var. name Obs.  mean    median s.d.    min.   max.
1 code
2 age       11    45.73   47     24.11   6      80
3 ht        11    157.18  160    14.3    120    172
4 wt        11    54.18   53     12.87   22     71
5 money     11    1023.18 500    1499.55 5      5000
6 sex       11    1.364   1      0.505   1      2
```

As mentioned in the previous chapter, the command *`summ`* gives summary statistics of all variables in the default data frame, in this case **`.data`**. Each of the six variables has 11 observations, which means that there are no missing values in the dataset. Since the variable 'code' is class 'character' (as shown from the '*`des()`*' command above), information about this variable is not shown. The ages of the subjects in this dataset range from 6 to 80 (years). Their heights range from 120 to 172 (cm), and their weights range from 22 to 71 (kg). The variable 'money' ranges from 5 to 5,000 (baht). The mean and median age, height and weight are quite close together indicating relatively non-skewed distributions. The variable 'money' has a mean much larger than the median signifying that the distribution is right skewed. The last variable, 'sex', is a factor. However, the statistics are based on the *unclassed* values of this variable. We can see that there are two levels, since the minimum is 1 and the maximum is 2. For factors, all values are stored internally as integers, i.e. only 1 or 2 in this case. The mean of 'sex' is 1.364 indicating that 36.4 percent of the subjects have the second level of the factor (in this case it is male). If a factor has more than two levels, the mean will have no useful interpretation.

Codebook

The function *`summ`* gives summary statistics of each variable, line by line. This is very useful for numeric variables but less so for factors, especially those with more than two levels. Epicalc has another function that gives summary statistics for a numeric variable and a frequency table with level labels and codes for factors.

```
> codebook()

 Anthropometric and financial data of a hypothetical family

code     :
A character vector
 ==================
age      :       Age(yr)
  obs. mean   median  s.d.   min.   max.
  11   45.727 47      24.11  6      80
 ==================
ht       :       Ht(cm.)
  obs. mean    median  s.d.   min.   max.
  11   157.182 160     14.3   120    172
 ==================
wt       :       Wt(kg.)
  obs. mean   median  s.d.   min.   max.
  11   54.182 53      12.87  22     71
 ==================
money    :       Pocket money(B.)
  obs. mean     median  s.d.    min.   max.
  11   1023.182 500     1499.55 5      5000
 ==================
sex      :
Label table: sex1
  code Frequency Percent
F    1         7    63.6
M    2         4    36.4
 ==================
```

Unlike results from the *summ* function, *codebook* deals with each variable in the data frame with more details. If a variable label exists, it is given in the output. For factors, the name of the table for the label of the levels is shown and the codes for the levels are displayed in the column, followed by frequency and percentage of the distribution. The function is therefore very useful. The output can be used to write a table of baseline data of the manuscript coming out from the data frame.

The output combines variable description with summary statistics for all numeric variables. For 'sex', which is a factor, the original label table is named 'sex1' where 1 = F and 2 = M. There are 7 females and 4 males in this family.

Note that the label table for codes of a factor could easily be done in the phase of preparing data entry using Epidata with setting of the ".chk" file. If the data is exported in Stata format, then the label table of each variable will be exported along with the dataset. The label tables are passed as attributes in the corresponding data frame. The Epicalc *codebook* command fully utilizes this attribute allowing users to see and document the coding scheme for future referencing.

We can also explore individual variables in more detail with the same commands *des* and *summ* by placing the variable name inside the brackets.

```
> des(code)

'code' is a variable found in the following source(s):

 Var. source  Var. order Class     # records Description
 .data        1          character 11
```

The output tells us that 'code' is in **.data**. Suppose we create an object, also called 'code', but positioned freely outside the hidden data frame.

```
> code <- 1
> des(code)

'code' is a variable found in the following source(s):

 Var. source  Var. order Class      # records Description
 .GlobalEnv              numeric    1
 .data        1          character  11
```

The output tells us that there are two 'codes'. The first is the recently created object in the global environment. The second is the variable inside the data frame, **.data**. To avoid confusion, we will delete the recently created object 'code'.

```
> rm(code)
```

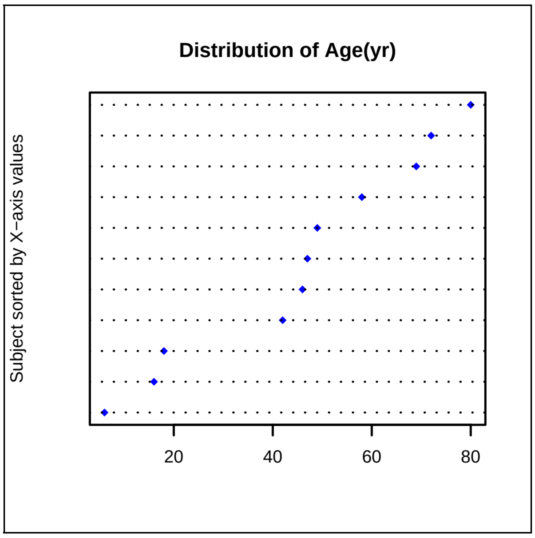
After removal of 'code' from the global environment, the latest *des()* command will describe the old 'code' variable, which is the part of **.data**, and remains usable. Using *des()* with other variables shows similar results.

Now try the following command:

```
> summ(code)
```

This gives an error because 'code' is a character object. Next type:

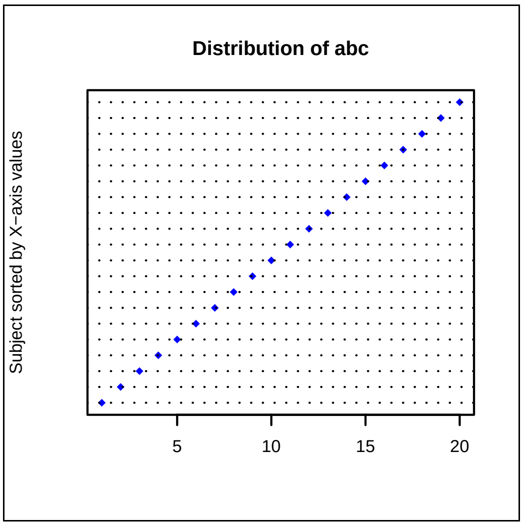
```
> summ(age)
  Obs.   mean   median  s.d.   min.   max.
  11     45.727 47      24.11  6      80
```



The results are similar to what we saw from *summ*. However, since the argument to the *summ* command is a single variable a graph is also produced showing the distribution of age.

The main title of the graph contains a description of the variable after the words "Distribution of". If the variable has no description, the variable name will be presented instead. Now try the following commands:

```
> abc <- 1:20
> summ(abc)
  Obs.  mean   median  s.d.   min.   max.
    20    10.5   10.5    5.916  1      20
```



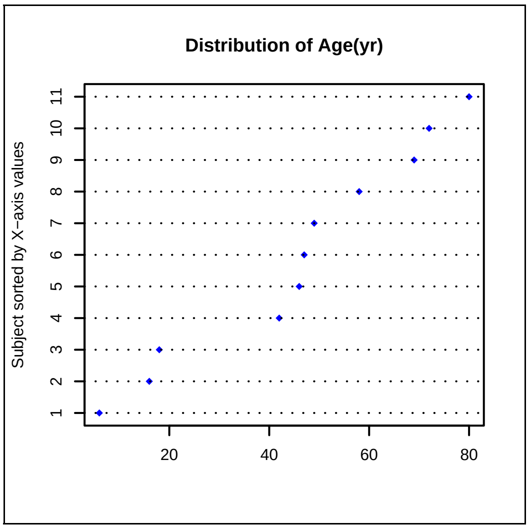
The object '`abc`' has a perfectly uniform distribution since the dots form a straight line.

The graph produced by the command *summ* is called a sorted dot chart. A dot chart has one axis (in this case the X-axis) representing the range of the variable. The other axis, the Y-axis, labelled 'Subject sorted by X-axis values', represents each subject or observation sorted by the values of the variable. For the object '`abc`', the smallest number is 1, which is plotted at the bottom left, then 2, 3, 4 etc. The final observation is 20, which is plotted at the top right. The values increase from one observation to the next higher value. Since this increase is steady, the line is perfectly straight.

To look at a graph of age again type:

```
> summ(age)
> axis(side=2, 1:length(age))
```

The 'axis' command adds tick marks and value labels on the specified axis (in this case, 'side=2' denotes the Y-axis). The ticks are placed at values of 1, 2, 3, up to 11 (which is the length of the vector age). The ticks are omitted by default since if the vector is too long, the ticks would be too congested. In this session, the ticks will facilitate discussion.



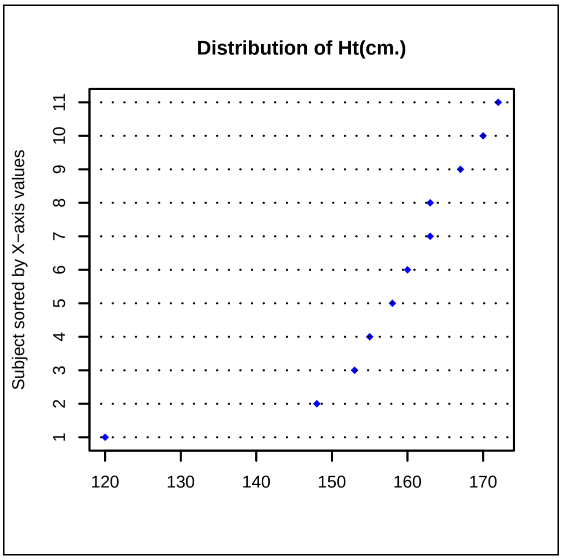
To facilitate further detailed consideration, the sorted age vector is shown with the graph.

```
> sort(age)
 [1]  6 16 18 42 46 47 49 58 69 72 80
```

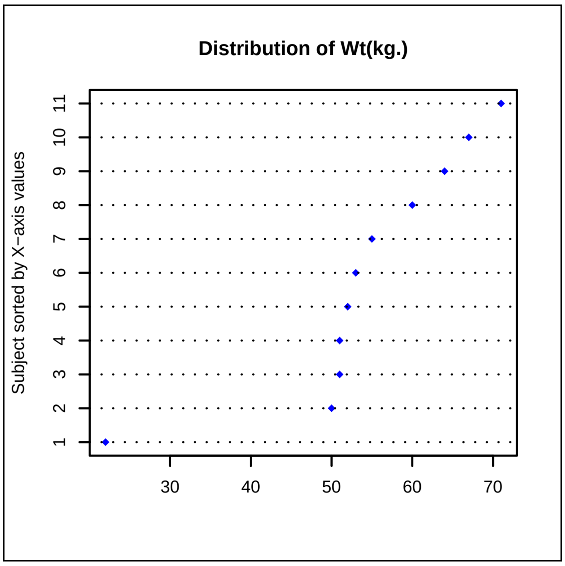
The relative increment on the X-axis from the first observation (6 years) to the second one (16 years) is larger than from the second to the third (18 years). Thus we observe a steep increase in the Y-axis for the second pair. From the 3rd observation to the 4th (42 years), the increment is even larger than the 1st one; the slope is relatively flat. In other words, there is no dot between 20 and 40 years. The 4th, 5th, 6th and 7th values are relatively close together, thus these give a relatively steep increment on the Y-axis.

```
> summ(ht)
  Obs.  mean    median  s.d.   min.   max.
  11    157.182 160     14.303 120    172
> axis(side=2, 1:length(ht))
> sort(ht)
 [1] 120 148 153 155 158 160 163 163 167 170 172
```

The distribution of height as displayed in the graph is interesting. The shortest subject (120cm) is much shorter than the remaining subjects. In fact, she is a child whereas all the others are adults. There are two persons (7th and 8th records) with the same height (163cm). The increment on the Y-axis is hence vertical.



```
> summ(wt)
> axis(side=2, 1:length(wt))
```

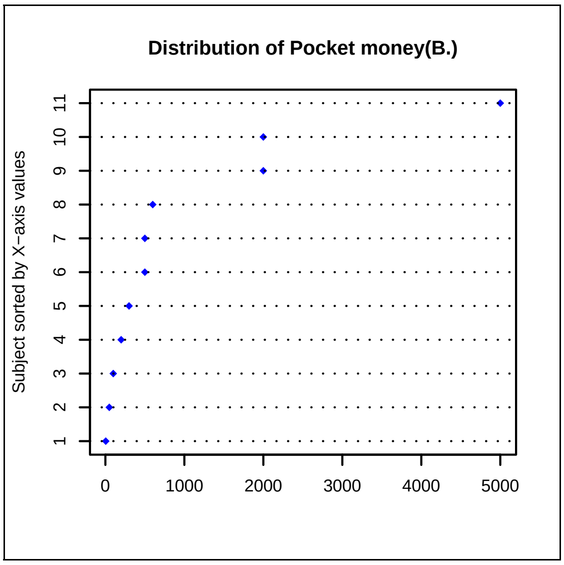


There is a higher level of clustering of weight than height from the 2nd to 7th observations; these six persons have very similar weights. From the 8th to 11th observations, the distribution is quite uniform.

For the distribution of the money variable, type:

```
> summ(money)
```

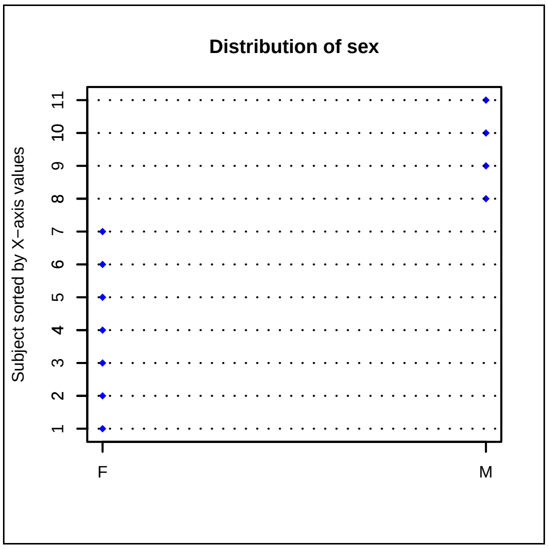
Money has the most skewed distribution. The first seven persons carry less than 1,000 baht. The next two persons carry around 2,000 baht whereas the last carries 5,000 baht, far away (in the X-axis) from the others. This is somewhat consistent with a theoretical exponential distribution.



Next have a look at the distribution of the sex variable.

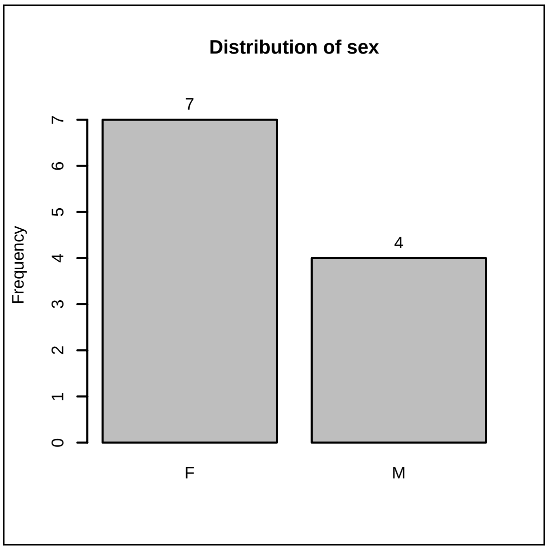
```
> summ(sex)
  Obs.   mean   median  s.d.   min.   max.
  11     1.364  1       0.5    1      2
```

The graph shows that four out of eleven (36.4%, as shown in the textual statistics) are male. When the variable is factor and has been labelled, the values will show the name of the group.



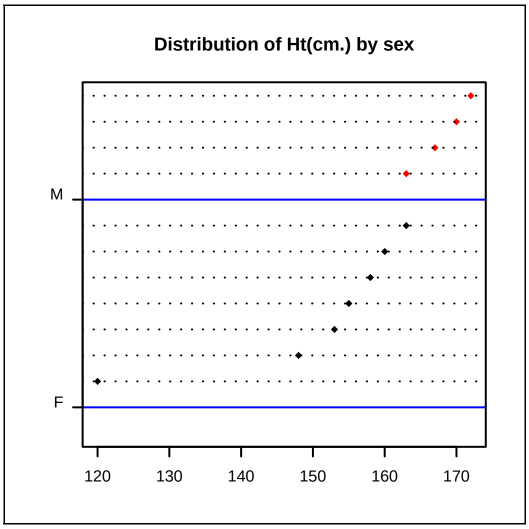
In fact, a better result can be obtained by typing

```
> tab1(sex)
sex :

        Frequency Percent Cum. percent
F               7    63.6         63.6
M               4    36.4        100.0
  Total        11   100.0        100.0
```



Since there are two sexes, we may simply compare the distributions of height by sex.

```
> summ(ht, by=sex)
For sex = F
  Obs.   mean    median   s.d.   min.    max.
  7      151     155      14.514 120     163

For sex = M
  Obs.   mean    median   s.d.   min.    max.
  4      168     168.5    3.916  163     172
```



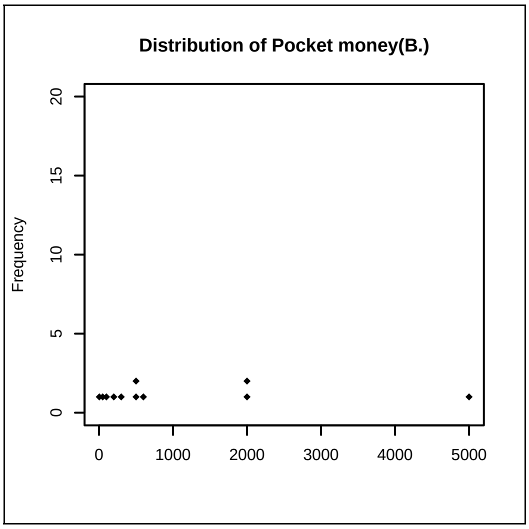
Clearly, males are taller than females.

Dotplot

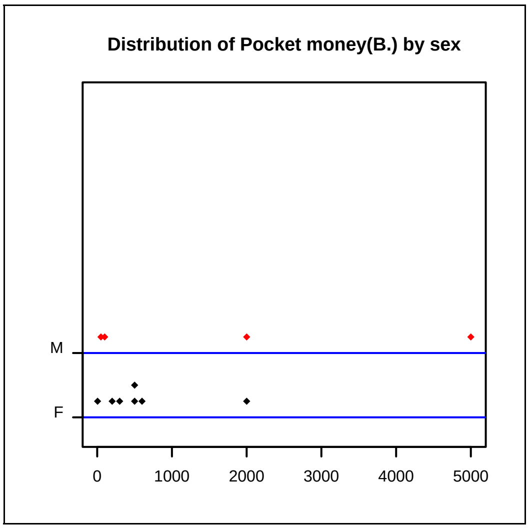
In addition to `summ` and `tab1`, *Epicalc* has another exploration tool called `dotplot`.

```
> dotplot(money)
```

While the graph created from the `summ` command plots individual values against its rank, `dotplot` divides the scale into several small equally sized bins (default = 40) and stacks each record into its corresponding bin. In the figure above, there are three observations at the leftmost bin and one on the rightmost bin. The plot is very similar to a histogram except that the original values appear on the X-axis. Most people are more acquainted with a dot plot than the sorted dot chart produced by `summ`. However, the latter plot gives more detailed information with better accuracy. When the sample size is small, plots by `summ` are more informative. When the sample size is large (say above 200), `dotplot` is more understandable by most people.



```
> dotplot(money, by=sex)
```



The command *summ* easily produces a powerful graph. One may want to show even more information. **R** can serve most purposes, but the user must spend some time learning it.

Let's draw a sorted dot chart for the heights. The command below should be followed step by step to see the change in the graphic window resulting from typing in each line. If you make a serious mistake simply start again from the first line. Using the up arrow key, the previous commands can be edited before executing again.

```
> zap()
> data(Familydata)
> use(Familydata)
> sortBy(ht)
> .data
```

The command `sortBy`, unlike its equivalent `sort` from the **base** library, has a permanent effect on **`.data`**. The whole data frame has been sorted in ascending order by the value of height.

```
> dotchart(ht)
```

Had the data not been sorted, the incremental pattern would not be seen.

```
> dotchart(ht, col=unclass(sex), pch=18)
```

Showing separate colours for each sex is done using the '`unclass`' function. Since 'sex' is a factor, uclassing it gives a numeric vector with 1 for the first level (female) and 2 for the second level (male). Colours can be specified in several different ways in **R**. One simple way is to utilise a small table of colours known as the *palette*. The default palette has 9 colours, where the number 1 represents black, the number 2 represents the red, up to 9, which represents gray. Thus the black dots represent females and the red dots represent males. More details on how to view or manipulate the palette can be found in the help pages.

To add the y-axis, type the following command:

```
> axis(side=2,at=1:length(ht), labels=code, las=1)
```

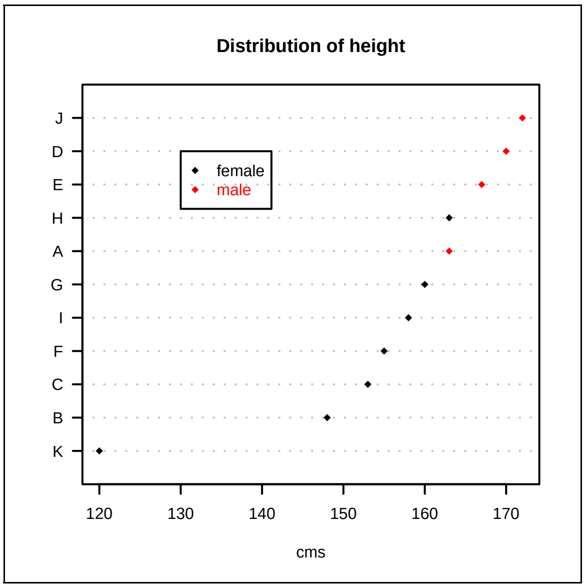
The argument 'las' is a graphical parameter, which specifies the orientation of tick labelling on the axes. When '`las=1`', all the labels of the ticks will be horizontal to the axis. A legend is added using the '`legend`' command:

```
> legend(x=130, y=10, legend=c("female","male"), pch=18,
  col=1:2, text.col=1:2)
```

The argument 'pch' stands for point or plotting character. Code 18 means the symbol is a solid diamond shape which is more prominent than `pch=1` (a hollow round dot). Note that 'col' is for plot symbol colours and 'text.col' is for text colour in the legend.

To add the titles type:

```
> title(main="Distribution of height")
> title(xlab="cms")
```



To summarise, after *use*(datafile), *des* and *summ*, individual variables can be explored simply by *summ*(var.name) and *summ*(var.name, by=group.var). In addition to summary statistics, the sorted dot chart can be very informative. The *dotplot* command trades in accuracy of the individual values with frequency dot plots, which is similar to a histogram. Further use of this command will be demonstrated when the number of observations is larger.

Exercise

Try the following simulations for varying sample sizes and number of groups. Compare the graph of different types from using three commands, summ, dotplot and boxplot. For each condition, which type of graph is the best?

Small sample size, two groups.

```
> grouping1 <- rep(1:2, times=5)
> random1   <- rnorm(10, mean=grouping1, sd=1)
> summ(random1, by=grouping1)
> dotplot(random1, by=grouping1)
> boxplot(random1 ~ grouping1)
```

Moderate sample size, three groups.

```
> grouping2 <- c(rep(1, 10),rep(2, 20), rep(3, 45))
> random2   <- rnorm(75, mean=grouping2, sd=1)
> summ(random2, by=grouping2)
> dotplot(random2, by=grouping2)
> boxplot(random2 ~ grouping2, varwidth=TRUE, col=1:3,
  horizontal=TRUE, las=1)
```

Large sample size, four groups.

```
> grouping3 <- c(rep(1, 100), rep(2, 200), rep(3,450), rep(4,
  1000))
> random3   <- rnorm(1750, mean=grouping3, sd=1)
> summ(random3, by=grouping3)
> dotplot(random3, by=grouping3)
> boxplot(random3 ~ grouping3, varwidth=TRUE, col=1:4,
  horizontal=TRUE, las=1)
```

Which kind of graph is the best for the different conditions?

Chapter 6: Date and Time

One of the purposes of an epidemiological study is to describe the distribution of a population's health status in terms of time, place and person. Most data analyses, however deal more with a person than time and place. In this chapter, the emphasis will be on time.

The time unit includes century, year, month, day, hour, minute and second. The most common unit that is directly involved in epidemiological research is day. The chronological location of day is date, which is a serial function of year, month and day.

There are several common examples of the use of dates in epidemiological studies. Birth date is necessary for computation of accurate age. In an outbreak investigation, description of date of exposure and onset is crucial for computation of incubation period. In follow up studies, the follow-up time is usually marked by date of visit. In survival analysis, date starting treatment and assessing outcome are elements needed to compute survival time.

Computation functions related to date

Working with dates can be computationally complicated. There are leap years, months with different lengths, days of the week and even leap seconds. Dates can even be stored in different eras depending on the calendar. The basic task in working with dates is to link the time from a fixed date to the display of various date formats that people are familiar with.

Different software use different starting dates for calculating dates. This is called an *epoch*. **R** uses the first day of 1970 as its epoch (day 0). In other words, dates are stored as the number of days since 1st January 1970, with negative values for earlier dates. Try the following at the **R** console:

```
> a <- as.Date("1970-01-01")
> a
[1] "1970-01-01"
> class(a)
[1] "Date"
> as.numeric(a)
[1] 0
```

The first command above creates an object 'a' with class *Date*. When converted to numeric, the value is 0. Day 100 would be

```
> a + 100
[1] "1970-04-11"
```

The default display format in **R** for a *Date* object is ISO format. The American format of 'month, day, year' can be achieved by

```
> format(a, "%b %d, %Y")
[1] "Jan 01, 1970"
```

The function 'format' displays the object 'a' in a fashion chosen by the user. '%b' denotes the month in the three-character abbreviated form. '%d' denotes the day value and '%Y' denotes the value of the year, including the century.

Under some operating system conditions, such as the Thai Windows operating system, '%b' and '%a' may not work or may present some problems with fonts. Try the following command:

```
> Sys.setlocale("LC_ALL", "C")
```

Now try the above format command again. This time, it should work. **R** has the 'locale' or working location set by the operating system, which varies from country to country. "C" is the motherland of **R** and the language "C" is American English. '%A' and '%a' are formats representing full and abbreviated weekdays, respectively, while '%B' and '%b' represent the months. These are language and operating system dependent.

Try these:

```
> b <- a + (0:3)
> b
```

Then change the language and see the effect on the **R** console and graphics device.

```
> setTitle("German"); summ(b)
> setTitle("French"); summ(b)
> setTitle("Italian"); summ(b)
```

The command *setTitle* changes the locale as well as the fixed wording of the locale to match it. To see what languages are currently available in Epicalc try:

```
> titleString()
> titleString(return.look.up.table=TRUE)
```

Note that these languages all use standard ASCII text characters. The displayed results from these commands will depend on the operating system. Thai and Chinese versions of Windows may give different results.

You may try *setTitle* with different locales. To reset the system to your original default values, type

```
> setTitle("")
```

For languages with non-standard ASCII characters, the three phrases often used in Epicalc ("Distribution of", "by", and "Frequency") can be changed to your own language. For more details see the help for the *titleString* function.

Manipulation of title strings, variable labels and levels of factors using your own language means you can have the automatic graphs tailored to your own needs. This is however a bit too complicated to demonstrate in this book. Interested readers can contact the author for more information.

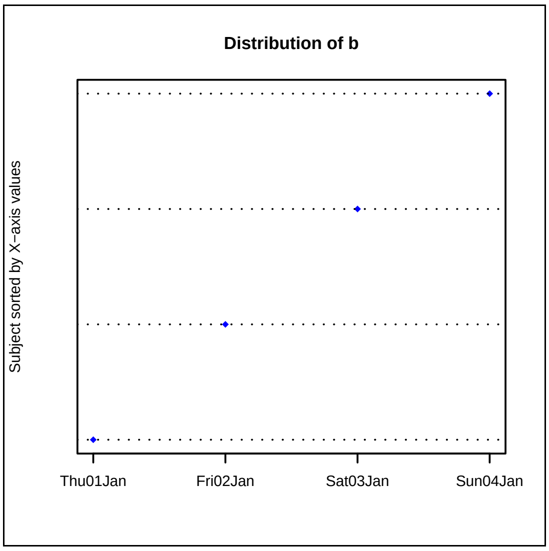
Epicalc displays the results of the *summ* function in ISO format to avoid country biases. The graphic results in only a few range of days, like the vector 'b', has the X-axis tick mark labels in '%a%d%b' format. Note that '%a' denotes weekday in the three-character abbreviated form.

In case the dates are not properly displayed, just solve the problem by typing:

```
> Sys.setlocale("LC_ALL", "C")
```

Then, check whether the date format containing '%a' and '%b' works.

```
> format(b, "%a %d%b%y")
[1] "Thu 01Jan70" "Fri 02Jan70" "Sat 03Jan70" "Sun 04Jan70"

> summ(b)
  obs. mean       median     s.d.   min.       max.
  4    1970-01-02 1970-01-02 <NA>   1970-01-01 1970-01-04
```



Reading in a date variable

Each software has its own way of reading in dates. Transferring date variables from one software to another sometimes results in 'characters' which are not directly computable by the destination software.

R can read in date variables from Stata files directly but not older version of EpiInfo with <dd/mm/yy> format. This will be read in as 'character' or 'AsIs'.

When reading in data from a comma separated variable (.csv) file format, it is a good habit to put an argument 'as.is = TRUE' in the `read.csv` command to avoid date variables being converted to factors.

It is necessary to know how to create date variables from character format. Create a vector of three dates stored as character:

```
> date1 <- c("07/13/2004","08/01/2004","03/13/2005")
> class(date1)
[1] "character"

> date2 <- as.Date(date1, "%m/%d/%Y")
```

The format or sequence of the original characters must be reviewed. In the first element of '`date1`', '13', which can only be day (since there are only 12 months), is in the middle position, thus '%d' must also be in the middle position. Slashes '/' separate month, day and year. This must be correspondingly specified in the format of the `as.Date` command.

```
> date2
[1] "2004-07-13" "2004-08-01" "2005-03-13"

> class(date2)
[1] "Date"
```

The default date format is "%Y-%m-%d". Changing into the format commonly used in *Epicalc* is achieved by:

```
> format(date2, "%d%b%y")
[1] "13Jul04" "01Aug04" "13Mar05"
```

Other formats can be further explored by the following commands:

```
> help(format.Date)
> help(format.POSIXct)
```

It is not necessary to have all day, month and year presented. For example, if only month is to be displayed, you can type:

```
> format(date2, "%B")
[1] "July"   "August" "March"
```

To include day of the week:

```
> format(date2, "%a-%d%b")
[1] "Tue-13Jul" "Sun-01Aug" "Sun-13Mar"

> weekdays(date2)
[1] "Tuesday" "Sunday"  "Sunday"
```

This is the same as

```
> format(date2, "%A")
```

Conversely, if there are two or more variables that are parts of date:

```
> day1 <- c("12","13","14");
> month1 <- c("07","08","12")
> paste(day1, month1)
[1] "12 07" "13 08" "14 12"

> as.Date(paste(day1,month1), "%d %m")
[1] "2007-07-12" "2007-08-13" "2007-12-14"
```

The function `paste` joins two character variables together. When the year value is omitted, **R** automatically adds the current year of the system in the computer.

Dealing with time variables

A *Date* object contains year, month and day values. For time, values of hour, minute and second must be available.

A sample dataset involving a number of timing variables was collected from participants of a workshop on 14th December 2004, asking about personal characteristics, times they went to bed, woke up, and arrived at the workshop. The workshop commenced at 8.30 am.

```
> zap()
> data(Timing)
> use(Timing)
```

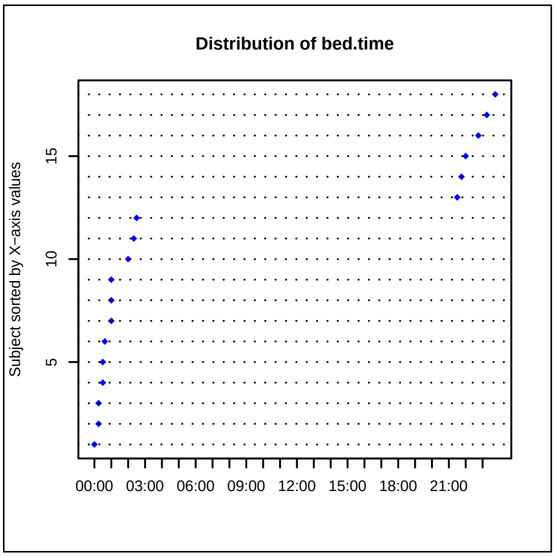
Note:

The original file for this dataset is in Stata format and is called "**timing.dta**". If you have downloaded this file into the working directory (as explained in the previous chapter), you may simply type `use("timing.dta")`.

```
> des()

Timing questionnaire
No. of observations =18

   Variable      Class          Description
1  id            integer
2  gender        factor
3  age           integer
4  marital       factor
5  child         integer        No. of children
6  bedhr         integer        Hour to bed
7  bedmin        integer        Min. to bed
8  wokhr         integer        Hour woke up
9  wokmin        integer        Min. woke up
10 arrhr         integer        Hour arrived at wkshp
11 arrmin        integer        Min. arrived at wkshp

> summ()

Timing questionnaire

No. of observations = 18

   Var. name Obs.  mean   median  s.d.   min.   max.
1  id        18    9.5    9.5     5.34   1      18
2  gender    18    1.611  2       0.502  1      2
3  age       18    31.33  27.5    12.13  19     58
4  marital   18    1.611  2       0.502  1      2
5  child     18    0.33   0       0.59   0      2
6  bedhr     18    7.83   1.5     10.34  0      23
7  bedmin    18    19.83  17.5    17.22  0      45
8  wokhr     18    5.61   6       1.61   1      8
9  wokmin    18    23.83  30      17.2   0      49
10 arrhr     18    8.06   8       0.24   8      9
11 arrmin    18    27.56  29.5    12.72  0      50
```

To create a variable equal to the time the participants went to bed, the function `ISOdatetime` is used.

```
> bed.time <- ISOdatetime(year=2004, month=12, day=14,
  hour=bedhr, min=bedmin, sec=0, tz="")

> summm(bed.time)
           Min.             Median               Mean                Max.
2004-12-14 00:00 2004-12-14 01:30 2004-12-14 08:09 2004-12-14 23:45
```

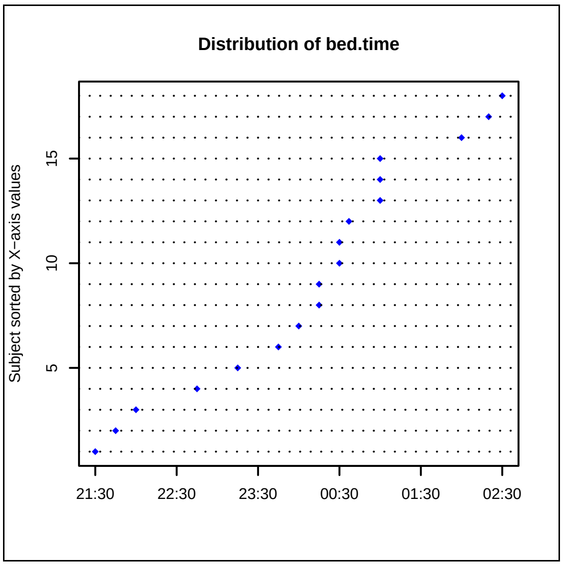


The graph shows interrupted time. In fact, the day should be calculated based on the time that the participants went to bed. If the participant went to bed between 12pm (midday) and 12am (midnight), then the day should be December 13th, otherwise the day should be the 14th, the day of the workshop. To recalculate the day type:

```
> bed.day <- ifelse(bedhr > 12, 13, 14)
```

The `ifelse` function chooses the second argument if the first argument is TRUE, the third otherwise.

```
> bed.time <- ISOdatetime(year=2004, month=12, day=bed.day,
  hour=bedhr, min=bedmin, sec=0, tz="")

> summ(bed.time)
           Min.             Median               Mean                Max.
2004-12-13 21:30 2004-12-14 00:22 2004-12-14 00:09 2004-12-14 02:30
```

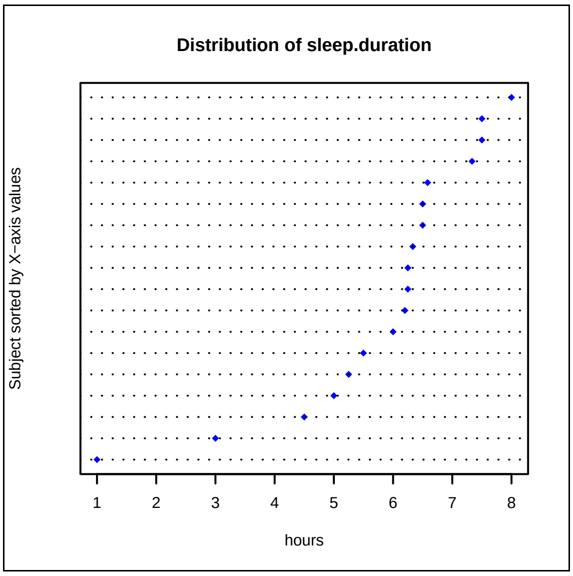


After this, woke up time and arrival time can be created and checked.

```
> woke.up.time <- ISOdatetime(year=2004, month=12, day=14,
  hour=wokhr, min=wokmin, sec=0, tz="")

> summ(woke.up.time)
           Min.            Median              Mean              Max.
2004-12-14 01:30 2004-12-14 06:10 2004-12-14 06:00 2004-12-14 08:20
```

The object 'woke.up.time' looks normal, although one or two participants woke up quite early in the morning. To compute sleeping duration type:

```
> sleep.duration <- difftime(woke.up.time, bed.time)

> summ(sleep.duration)
  Obs.   mean   median  s.d.   min.   max.
  18     5.844  6.25    1.7    1      8
```



A suitable choice of units for '`sleep.duration`' are chosen, but can be changed by the user if desired. Somebody slept very little.

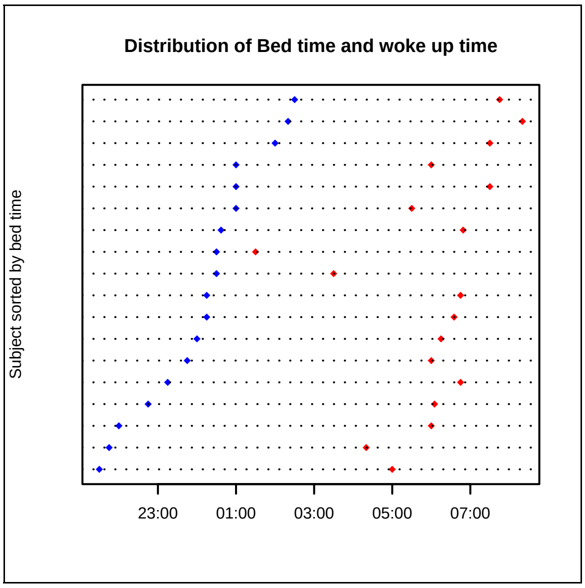
Displaying two variables in the same graph

The command `summ` of *Epicalc* is not appropriate for displaying two variables simultaneously. The original dotchart of **R** is the preferred graphical method.

```
> sortBy(bed.time)
> plot(bed.time, 1:length(bed.time),
  xlim=c(min(bed.time),max(woke.up.time)), pch=18, col="blue",
  ylab=" ", yaxt="n")
```

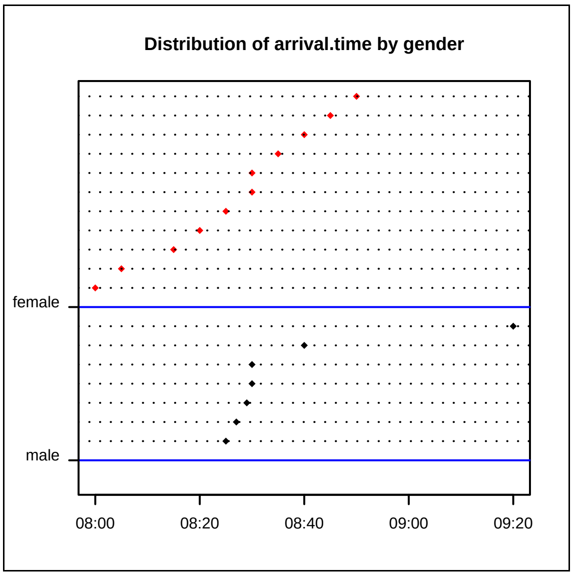
The argument 'xlim' (x-axis limits) is set to be the minimum of '`bed.time`' and the maximum of '`woke.up.time`'. The argument yaxt="n" suppresses the tick labels on the Y-axis.

```
> n <- length(bed.time)
> segments(bed.time, 1:n, woke.up.time, 1:n)
> points(woke.up.time, 1:n, pch=18, col="red")
> title(main="Distribution of Bed time and Woke up time")
```



Finally, arrival time at the workshop is created:

```
> arrival.time <- ISOdatetime(year=2004, month=12, day=14,
  hour=arrhr, min=arrmin, sec=0, tz="")

> summ(arrival.time)
            Min.           Median               Mean               Max.
2004-12-14 08:00 2004-12-14 08:30 2004-12-14 08:30 2004-12-14 09:20

> summ(arrival.time, by=gender)

For gender = male
            Min.           Median               Mean               Max.
2004-12-14 08:25 2004-12-14 08:30 2004-12-14 08:37 2004-12-14 09:20

For gender = female
            Min.           Median               Mean               Max.
2004-12-14 08:00 2004-12-14 08:30 2004-12-14 08:26 2004-12-14 08:50
```



The command *summ* works relatively well with time variables. In this case, it demonstrates that there were more females than males. Females varied their arrival time considerably. Quite a few of them arrived early because they had to prepare the workshop room. Most males who had no responsibility arrived just in time. There was one male who was slightly late and one male who was late by almost one hour.

Age and difftime

Computing age from birth date usually gives more accurate results than obtaining age from direct interview. The following dataset contains subject's birth dates that we can use to try computing age.

```
> zap()
> data(Sleep3)
> use(Sleep3)
> des()

Sleepiness among the participants in a workshop
No. of observations =15
  Variable     Class        Description
1 id           integer      code
2 gender       factor       gender
3 dbirth       Date         Date of birth
4 sleepy       integer      Ever felt sleepy in workshop
5 lecture      integer      Sometimes sleepy in lecture
6 grwork       integer      Sometimes sleepy in group work
7 kg           integer      Weight in Kg
8 cm           integer      Height in cm
```

The date of analysis was 13th December 2004.

```
> age <- as.Date("2004-12-13") - dbirth
```

The variable 'age' has class *difftime* as can be seen by typing:

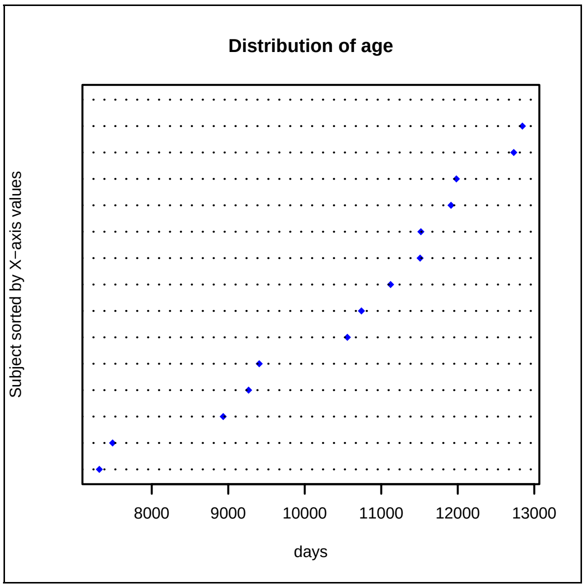
```
> class(age)
[1] "difftime"
```

The unit of age is 'days'.

```
> attr(age, "unit")
[1] "days"
```

To display age:

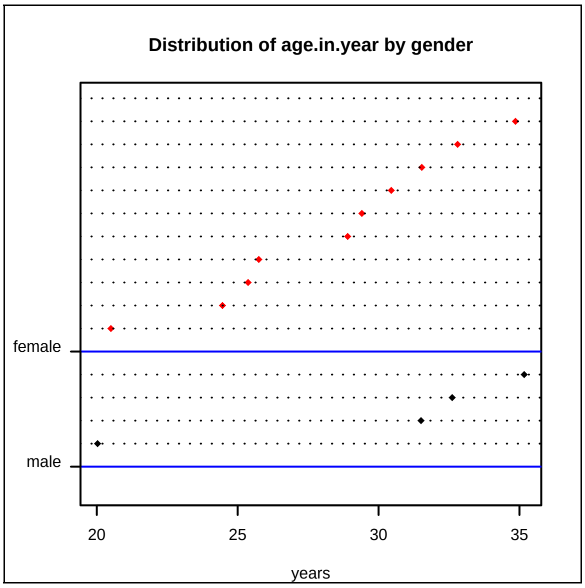
```
> age
Time differences of  7488, 10557,  8934,  9405, 11518, 11982,
  10741, 11122, 12845,  9266, 11508, 12732, 11912,  7315,
  NA days

> summ(age)
  Obs.   mean    median  s.d.     min.    max.
  15     10520   10930   1787.88  7315    12850
```



Note the one missing value. To convert age into years:

```
> age.in.year <- as.numeric(age)/365.25
> summ(age.in.year)
  Obs.   mean    median  s.d.   min.    max.
  14     28.81   29.93   4.89   20.03   35.17
```

```
> summ(age.in.year, by=gender)
For gender = male
  Obs.   mean   median  s.d.   min.   max.
  4      29.83  32.06   6.712  20.03  35.17

For gender = female
  Obs.   mean   median  s.d.   min.   max.
    10    28.4   29.16   4.353  20.5   34.86
```



Note that there is a blank dotted line at the top of the female group. This a missing value. Males have an obviously smaller sample size with the same range as women but most observations have relatively high values.

Exercises

In the `Timing` dataset:

Compute time since woke up to arrival at the workshop.

Plot time to bed, time woke up and arrival time on the same axis.

Chapter 7: An Outbreak Investigation: Describing Time

An outbreak investigation is a commonly assigned task to an epidemiologist. This chapter illustrates how the data can be described effectively. Time and date data types are not well prepared and must be further modified to suit the need of the descriptive analysis.

On 25 August 1990, the local health officer in Supan Buri Province of Thailand reported the occurrence of an outbreak of acute gastrointestinal illness on a national handicapped sports day. Dr Lakkana Thaikruea and her colleagues went to investigate. The dataset is called **`Outbreak`**.. Most variable names are self-explanatory. Variables are coded as 0 = no, 1 = yes and 9 = missing/unknown for three food items consumed by participants: 'beefcurry' (beef curry), 'saltegg' (salted eggs) and 'water'. Also on the menu were eclairs, a finger-shaped iced cake of choux pastry filled with cream. This variable records the number of pieces eaten by each participant. Missing values were coded as follows: 88 = "ate but do not remember how much", while code 90 represents totally missing information. Some participants experienced gastrointestinal symptoms, such as: nausea, vomiting, abdominal pain and diarrhea. The ages of each participant are recorded in years with 99 representing a missing value. The variables 'exptime' and 'onset' are the exposure and onset times, which are in character format, or 'AsIs' in **R** terminology.

Quick exploration

Let's look at the data. Type the following at the **R** console:

```
> zap()
> data(Outbreak)
> use(Outbreak)
> des()

No. of observations =1094
```

```
   Variable      Class           Description
1  id            numeric
2  sex           numeric
3  age           numeric
4  exptime       AsIs
5  beefcurry     numeric
6  saltegg       numeric
7  eclair        numeric
8  water         numeric
9  onset         AsIs
10 nausea        numeric
11 vomiting      numeric
12 abdpain       numeric
13 diarrhea      numeric

> summm()

No. of observations = 1094

   Var. name  valid obs. mean   median  s.d.    min.   max.
1  id         1094       547.5  547.5   315.95  1      1094
2  sex        1094       0.66   1       0.47    0      1
3  age        1094       23.69  18      19.67   1      99
4  exptime
5  beefcurry  1094       0.95   1       0.61    0      9
6  saltegg    1094       0.96   1       0.61    0      9
7  eclair     1094       11.48  2       27.75   0      90
8  water      1094       1.02   1       0.61    0      9
9  onset
10 nausea     1094       0.4    0       0.49    0      1
11 vomiting   1094       0.38   0       0.49    0      1
12 abdpain    1094       0.35   0       0.48    0      1
13 diarrhea   1094       0.21   0       0.41    0      1
```

We will first define the cases, examine the timing in this chapter and investigate the cause in the next section.

Case definition

It was agreed among the investigators that a case should be defined as a person who had any of the four symptoms: 'nausea', 'vomiting', 'abdpain' or 'diarrhea'. A case can then by computed as follows:

```
> case <- (nausea==1)|(vomiting==1)|(abdpain==1)|(diarrhea==1)
```

To incorporate this new variable into **`.data`**, we use the function *`label.var`*., which is explained in detail in chapter 10.

```
> label.var(case, "diseased")
```

The object '`case`' is now incorporated into **`.data`** as the 14th variable together with a variable description. Note that the class is *logical*.

```
> des()
```

Timing of exposure

For the exposure time, first look at the structure of this variable.

```
> str(exptime)
Class 'AsIs' chr [1:1094] "25330825180000" "25330825180000"...
```

The values of this variable contain fourteen digits. The first four digits represent the year of the outbreak in the Buddhist Era (B.E.) calendar, which is equal to A.D. + 543. The 5th and 6th digits contain the two digits representing the month, the 7th and 8th represent the day, 9th and 10th hour, 11th and 12th minute and 13th and 14th second.

```
> day.exptime <- substr(exptime, 7, 8)
```

The **R** command `susbtr` (from substring), extracts parts of character vectors. First, let's look at the day of exposure.

```
> tab1(day.exptime)
day.exptime :
        Frequency   %(NA+) cum.%(NA+)   %(NA-) cum.%(NA-)
25           1055     96.4       96.4      100        100
<NA>           39      3.6      100.0        0        100
  Total      1094    100.0      100.0      100        100
```

The day of exposure was 25th of August for all records (ignoring the 39 missing values). We can extract the exposure time in a similar fashion.

```
> hr.exptime <- substr(exptime, 9, 10)
> tab1(hr.exptime)
```

All values seem acceptable, with the mode at 18 hours.

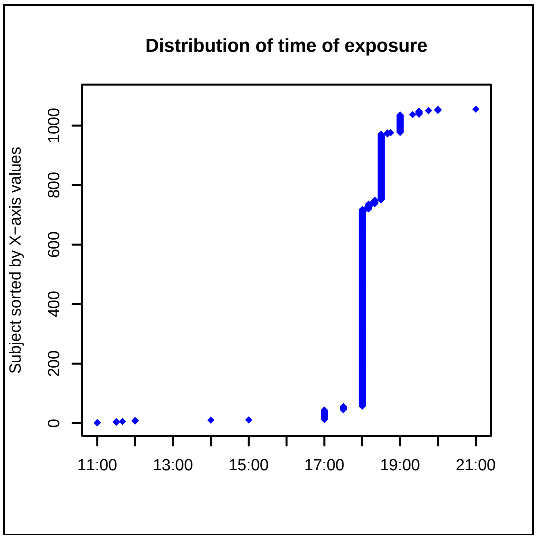
```
> min.exptime <- substr(exptime, 11, 12)
> tab1(min.exptime)
```

These are also acceptable, although note that most minutes have been rounded to the nearest hour or half hour. The time of exposure can now be calculated.

```
> time.expose <- ISOdatetime(year=1990, month=8, day=day.exptime,
  hour=hr.exptime, min=min.exptime, sec=0)
```

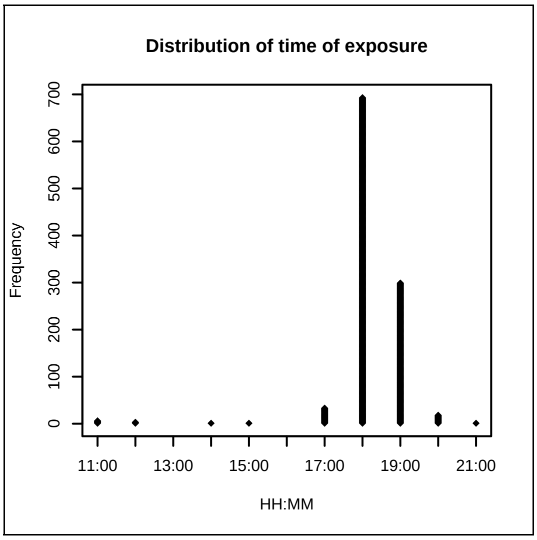
Then, the variable is labelled in order to integrate it into the default data frame.

```
> label.var(time.expose, "time of exposure")
> summ(time.expose)
          Min.           Median             Mean              Max.
1990-08-25 11:00 1990-08-25 18:00 1990-08-25 18:06  1990-08-25 21:00
```



A dotplot can also be produced.

```
> dotplot(time.expose)
```



Almost all the exposure times were during dinner; between 6 and 7 o'clock, while only a few were during the lunchtime.

Timing the onset

Exploration of the data reveals that three non-cases have non-blank onset times.

```
> sum(!is.na(onset[!case]))  # 3
```

The function `is.na` identifies the elements in the vector that have NA. For simplicitiy we make sure that the 'onset' variable is exclusively used for cases only.

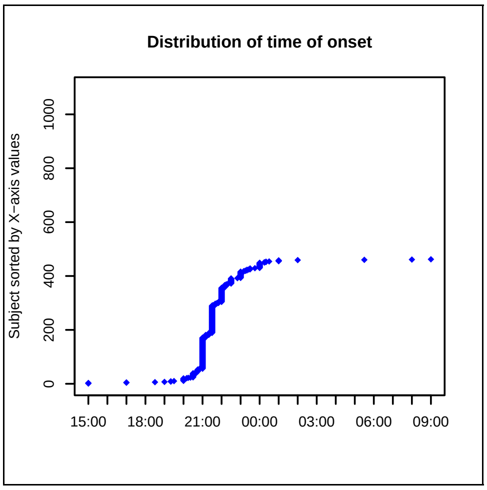
```
> onset[!case] <- NA
```

The extraction of symptom onset times is similar to that for time of exposure.

```
> day.onset <- substr(onset, 7, 8)
> tab1(day.onset)
day.onset :
        Frequency   %(NA+) cum.%(NA+)   %(NA-) cum.%(NA-)
25            429     39.2       39.2     92.9       92.9
26             33      3.0       42.2      7.1      100.0
<NA>          632     57.8      100.0      0.0      100.0
  Total      1094    100.0      100.0    100.0      100.0
```

Of the subjects interviewed, 57.8% had a missing 'onset' and subsequently on the derived variable 'day.onset'. This was due to either having no symptoms or the subject could not remember. Among those who reported the time, 429 had the onset on the 25th August. The remaining 33 had it on the day after.

```
> hr.onset <- substr(onset, 9, 10)
> tab1(hr.onset)
> min.onset <- substr(onset, 11, 12)
> tab1(min.onset)
> time.onset <- ISOdatetime(year=1990, month=8, day=day.onset,
  hour=hr.onset, min=min.onset, sec=0, tz="")
> label.var(time.onset, "time of onset")
> summ(time.onset)
```

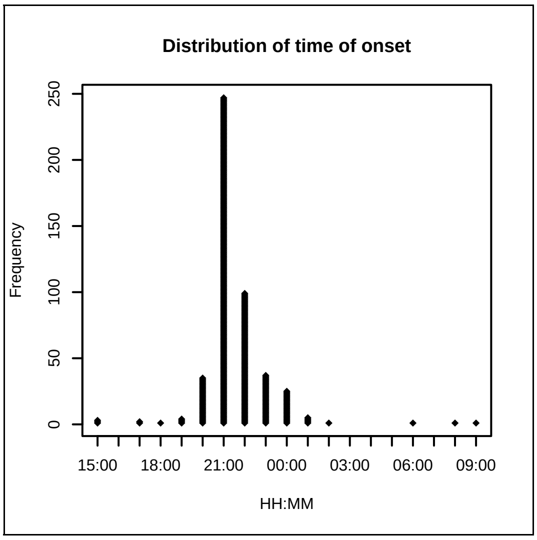


```
            Min.            Median              Mean                 Max.
1990-08-25 15:00 1990-08-25 21:30 1990-08-25 21:40  1990-08-26 09:00
```

The upper part of the graph is empty due to the many missing values.

Perhaps a better visual display can be obtained wth a dotplot.

```
> dotplot(time.onset)
```



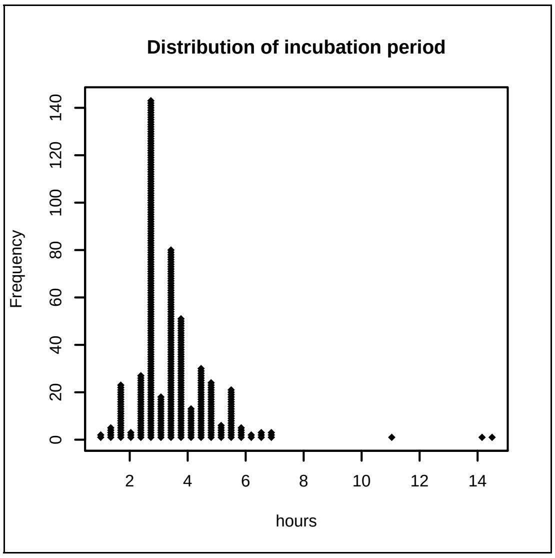
Both graphs show the classic single-peak epidemic curve, suggesting a single point source. The earliest case had the onset at 3pm in the afternoon of August 25. The majority of cases had the onset in the late evening. By the next morning, only a few cases were seen. The last reported case occurred at 9am on August 26.

Incubation period

The analysis for incubation period is straightforward.

```
> incubation.period <- time.onset - time.expose
> label.var(incubation.period, "incubation period")
> summ(incubation.period)
  Valid obs. mean   median  s.d.   min.   max.
  462        3.631  3.5     1.28   1      14.5
> dotplot(incubation.period, las=1)
```

Incubation period has a median of 3.5 hours with right skewness.



Paired plot

We now try putting the exposure and onset times in the same graph. A sorted graph usually gives more information, so the whole data frame is now sorted.

```
> sortBy(time.expose)
```

With this large sample size, it is better to confine the graph to plot only complete values for both 'time.exposure' and 'time.onset'. This subset is kept as another data frame called '`data.for.graph`'.

```
> data.for.graph <- subset(.data, (!is.na(time.onset) &
  !is.na(time.expose)), select = c(time.onset, time.expose))

> des(data.for.graph)
No. of observations =462
  Variable      Class           Description
1 time.onset    POSIXt
2 time.expose   POSIXt
```

There are only two variables in this data frame. All the missing values have been removed leaving 462 records for plotting.

```
> n <- nrow(data.for.graph)
> with(data.for.graph, {
   plot(time.expose, 1:n, col="red", pch=20,
   xlim = c(min(time.expose), max(time.onset)),
   main = "Exposure time & onset of food poisoning outbreak",
   xlab = "Time (HH:MM)", ylab = "Subject ID" )
  }  )
```

The plot pattern looks similar to that produced by *summ*(time.expose). The point character, 'pch', is set to 20, which plots small solid circles, thus avoiding too much overlapping of the dots. The limits on the horizontal axis are from the minimum of time of exposure to the maximum of the time of onset, allowing the points of onset to be put on the same graph. These points are added in the following command:

```
> with(data.for.graph, {
  points(time.onset, 1:n, col="blue", pch=20)
  } )
```

The two sets of points are paired by subjects. A line joining each pair is now drawn by the `segments` command.

```
> with(data.for.graph, {
  segments(time.expose, 1:n, time.onset, 1:n, col = "grey45")
  } )
```

The complete list of built in colour names used by **R** can be found from `colours()`.

A legend is inserted to make the graph self-explanatory.

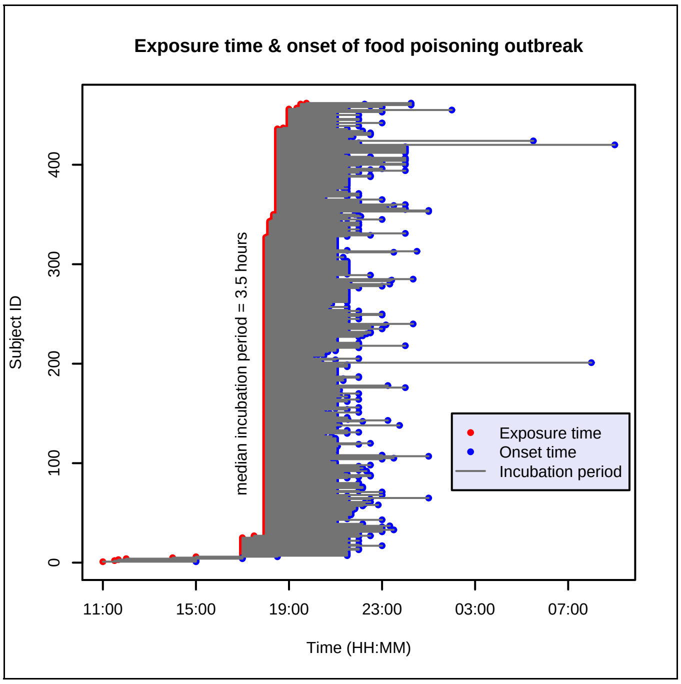
```
> legend(x = ISOdatetime(1990,8,26,2,0,0), y = 150,
  legend=c("Exposure time","Onset time","Incubation period"),
  pch=c(20,20,-1), lty=c(0,0,1),col=c("red","blue","grey45"),
  bg="lavender")
```

The left upper corner of the legend is located at the right lower quadrant of the graph with the x coordinate being 2am and y coordinate being 150. The legend consists of three items as indicated by the character vector. The point characters and colours of the legend are specified in accordance with those inside the graph. The last argument, incubation period, has 'pch' equal to -1 indicating no point is to be drawn. The line type, 'lty', of exposure and onset time are 0 (no line) whereas that for incubation period is 1 (solid line). The colours of the points and the lines are corresponding to that in the graph. The background of the legend was given lavender colour to supersede any lines or points behind the legend.

Finally, some text describing the key statistic of this variable is placed inside the plot area at 5pm and centred at 200.

```
> text(x = ISOdatetime(1990, 8, 25, 17, 0, 0), y = 200, labels
  = "median incubation period = 3.5 hours", srt = 90)
```

The middle of the text is located at x = 19:00 and y = 200 in the graph. The parameter 'srt' comes from 'string rotation'. In this case a rotation of 90 degrees gives the best picture. Since the background colour is already grey, white text would be suitable.



Analysis of timing data has finished. The main data frame **.data** is saved for further use in the next chapter.

```
> save(.data, file = "Chapter7.Rdata")
```

Reference

Thaikruea, L., Pataraarechachai, J., Savanpunyalert, P., Naluponjiragul, U. 1995 An unusual outbreak of food poisoning. Southeast Asian J Trop Med Public Health 26(1):78-85.

Exercise

We recode the original time variable 'onset' right from the beginning using the command:

```
> onset[!case] <- NA
```

For the data frame that we are passing to the next chapter, has the variable 'onset' been changed? If not, why and how can we get a permanent change to the data frame that we are using? Note: the built-in **`Outbreak`** dataset cannot be modified.

Chapter 8: An Outbreak Investigation: Risk Assessment

The next step in analysing the outbreak is to deal with the level of risk. However, let's first load the data saved from the preceding chapter.

```
> zap()
> load("Chapter7.Rdata")
> ls(all=TRUE)  # .data is there
> search()      # No dataset in the search path
> use(.data)
> search()      # .data is ready for use
> des()
```

Recoding missing values

There are a number of variables that need to be recoded. The first variable to recode is 'age'. The Epicalc command `recode` is used here. More details on this function are given in chapter 10.

```
> recode(var = age, old.value = 99, new.value = NA)
```

The variables with the same recoding scheme, 9 to missing value, are 'beefcurry', 'saltegg' and 'water'. They can be recoded together in one step as follows:

```
> recode(vars = c(beefcurry, saltegg, water), 9, NA)
```

The three variables can also be changed to factors with value labels attached.

```
> beefcurry <- factor(beefcurry, labels=c("No","Yes"))
> saltegg <- factor(saltegg, labels=c("No","Yes"))
> water <- factor(water, labels=c("No","Yes"))
> label.var(beefcurry, "Beefcurry")
> label.var(saltegg, "Salted egg")
> label.var(water, "Water")
```

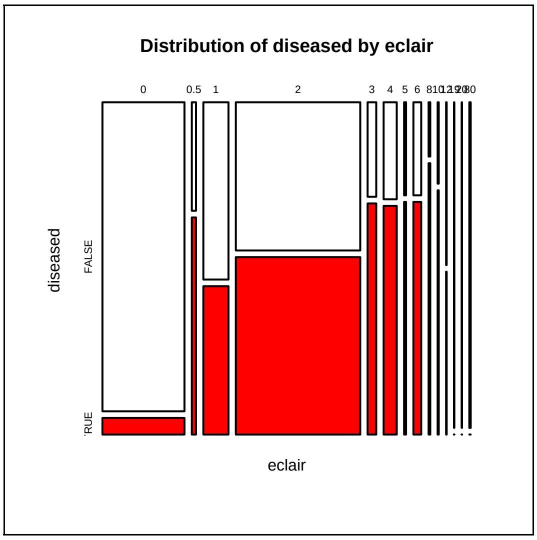
For 'eclair', the absolute missing value is 90. This should be recoded first, then re-check the data frame for the missing values.

```
> recode(eclair, 90, NA)
> summ()
```

All variables look fine except 'eclair' which still contains the value 80 representing "ate but not remember how much". We will analyse its relationship with 'case' by considering it as an ordered categorical variable.

At this stage, cross tabulation can be performed by using the *Epicalc* command `tabpct`.

```
> tabpct(eclair, case)
```



The width of the columns of the mosaic graph denotes the relative frequency of that category. The highest frequency is 2 pieces followed by 0 and 1 piece. The other numbers have relatively low frequencies; particularly the 5 records where 'eclair' was coded as 80.

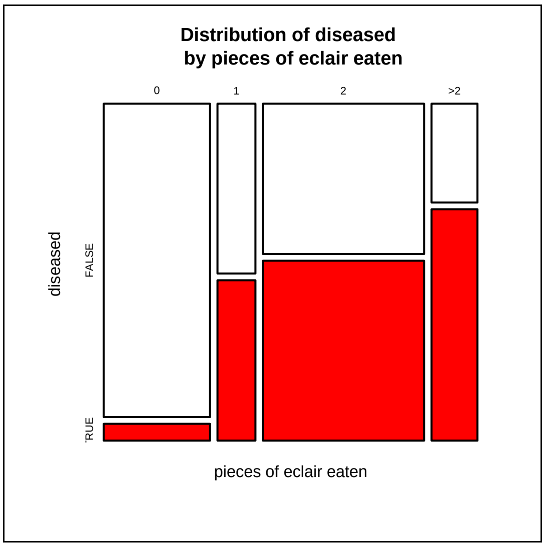
There is a tendency of increasing red area or attack rate from left to right indicating that the risk was increased when more pieces of eclair were consumed. We will use the distribution of these proportions to guide our grouping of eclair consumption. The first column of zero consumption has a very low attack rate, therefore it should be a separate category. Only a few took half a piece and this could be combined with those who took only one piece. Persons consuming 2 pieces should be kept as one category as their frequency is very high. Others who ate more than two pieces should be grouped into another category. Finally, those coded as '80' will be dropped due to the unknown amount of consumption as well as its low frequency.

```
> eclairgr <- cut(eclair, breaks = c(0, 0.4, 1, 2, 79),
  include.lowest = TRUE, labels=c("0","1","2",">2"))
```

The argument 'include.lowest' is set to TRUE to indicate that 0 eclair must be included in the lowest category.

It is a good practice to label the new variable in order to describe it as well as put it into **`.data`**. The *`label.var`* command is used to do this.

```
> label.var(eclairgr, "pieces of eclair eaten")
> tabpct(eclairgr, case)
======== lines omitted =========
Row percent
                      diseased
pieces of eclair eaten   FALSE    TRUE  Total
                    0      279      15    294
                        (94.9)   (5.1)  (100)
                    1       54      51    105
                        (51.4)  (48.6)  (100)
                    2      203     243    446
                        (45.5)  (54.5)  (100)
                    >2      38      89    127
                        (29.9)  (70.1)  (100)
 ======== lines omitted =========
```



The attack rate or percentage of diseased in each category of exposure, as shown in the bracket of the column TRUE, increases from 5.1% among those who did not eat any eclairs to 70.1% among those heavy eaters of eclair. The graph output is similar to the preceding one except that the groups are more concise.

We now have a continuous variable of 'eclair' and a categorical variable of 'eclairgr'. The next step is to create a binary exposure for eclair.

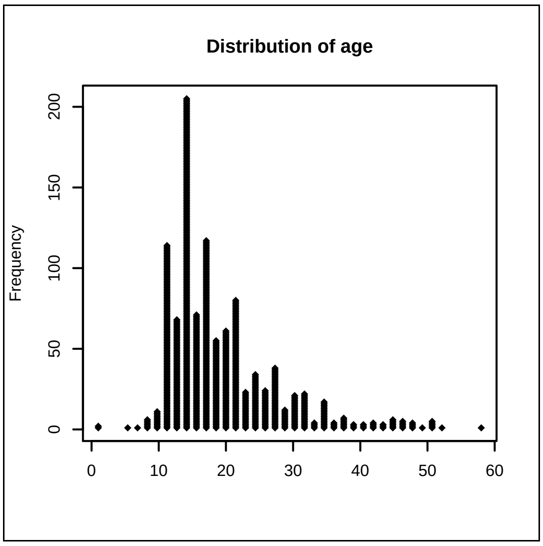
```
> eclair.eat <- eclair > 0
> label.var(eclair.eat, "eating eclair")
```

This dichotomous exposure variable is now similar to the others, ('beefcurry', 'saltegg' and 'water').

Exploration of age and sex

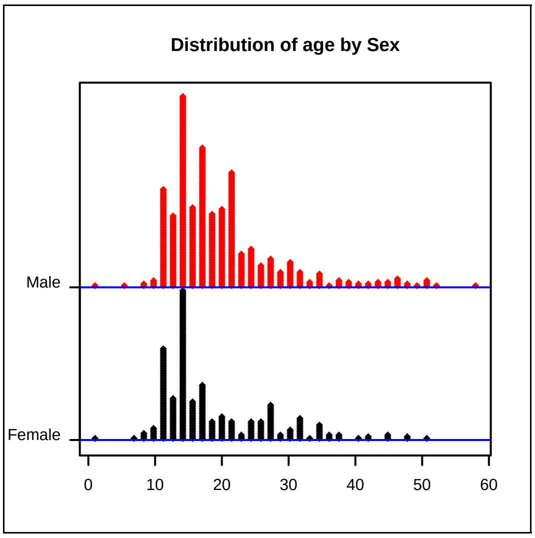
Simple exploration can be done by using the *summ* and *dotplot* commands on 'age', such as:

```
> summ(age); dotplot(age)
```



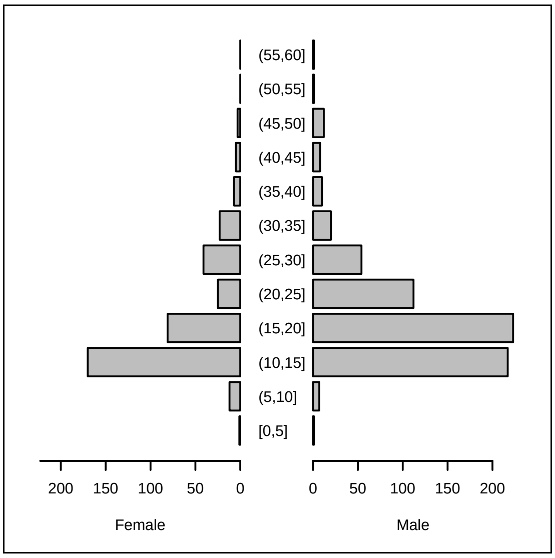
The age distribution classified by sex can easily be done via:

```
> sex <- factor(sex, labels=c("Female","Male"))
> summ(age, by = sex)
> dotplot(age, by = sex)
```



An alternative is to draw a population pyramid of age and sex, using the Epicalc function *pyramid*, as follows:

```
> pyramid(age, sex)
```



From the resulting graph, young adult males (aged 10-20 years) predominated. The binwidth can also be changed to have fewer age groups.

```
> pyramid(age, sex, binwidth = 15)
```

The table generated by the pyramid function can also be shown, as follows:

```
> pyramid(age, sex, printTable=TRUE)

Tabulation of age by sex (frequency).
         sex
age       Female Male
  [0,5]        1    1
  (5,10]      12    7
  (10,15]    170  217
  (15,20]     81  223
  (20,25]     25  112
  (25,30]     41   54
  (30,35]     23   20
  (35,40]      7   10
  (40,45]      5    8
  (45,50]      3   12
  (50,55]      0    1
  (55,60]      0    1
```

The percentage (for each sex) can also be shown.

```
> pyramid(age, sex, printTable=TRUE, percent="each")
```

```
 Tabulation of age by sex (percentage of each sex).
        Female   Male
[0,5]    0.272  0.150
(5,10]   3.261  1.051
(10,15] 46.196 32.583
(15,20] 22.011 33.483
(20,25]  6.793 16.817
(25,30] 11.141  8.108
(30,35]  6.250  3.003
(35,40]  1.902  1.502
(40,45]  1.359  1.201
(45,50]  0.815  1.802
(50,55]  0.000  0.150
(55,60]  0.000  0.150
```

Finally, both the table and age group can be saved as **R** objects for future use.

```
> (age.tab <- pyramid(age, sex))
> ageGrp <- age.tab$ageGroup
> label.var(ageGrp, "Age Group")
> des()
> des("age*")

No. of observations =1094
   Variable      Class          Description
3  age           numeric
20 ageGrp        factor         Age Group
```

The `des` function can also display variables using wild card matching.

```
> des("????????")

No. of observations =1094
   Variable      Class          Description
11 vomiting      numeric
13 diarrhea      numeric
18 eclairgr      factor         pieces of eclair eaten
```

We have spent some time learning these features of Epicalc for data exploration. Let's return to the analysis of risk, which is another main feature of Epicalc.

Comparison of risk: Risk ratio and attributable risk

There are basically two methods for comparing the risk of disease in different exposure groups.

Risk ratio – RR (also called relative risk) is the *ratio* of the risk of getting disease among the exposed compared with that among the non-exposed. It indicates how many times the risk would increase had the subject changed their status from non-exposed to exposed. The increment is considered in fold, thus has a mathematical notation of being a 'multiplicative model'.

Risk difference on the other hand, suggests the *amount* of risk gained or lost had the subject changed from non-exposed to exposed. The increase is absolute, and has the mathematical notation of an *additive* model.

The Epicalc command *cs* is used to analyse such relationships.

```
> cs(case, eclair.eat)

       eating eclair
case    FALSE TRUE Total
  FALSE 279   300  579
  TRUE  15    383  398
  Total 294   683  977

        Rne   Re   Rt
  Risk  0.05  0.56 0.41
                                      Estimate Lower95 Upper95
Risk difference (attributable risk)   0.51     0.44    0.58
Risk ratio                            10.99    8       15.1
Attr. frac. exp. -- (Re-Rne)/Re       0.91
Attr. frac. pop. -- (Rt-Rne)/Rt*100 % 87.48
```

'Rne', 'Re' and 'Rt' are the risks in the non-exposed, exposed and the total population, respectively. 'Rne' in this instance is 15/294 = 0.05. Similarly 'Re' is 383/683 = 0.56 and 'Rt' is 398/977 = 0.41. The risk difference is 'Re' - 'Rne', an absolute increase of 51% whereas the risk ratio is 'Re' / 'Rne', a increase of 11 fold. The risk of getting the disease among those eating eclairs could have been reduced by 91% and the risk among all participants in the sports carnival could have been reduced by 87.5% had they not eaten any eclairs.

The risk ratio is an important indicator for causation. A risk ratio above 10 would strongly suggest a causal relationship.

The risk difference has more public health implications than the risk ratio. A high risk ratio may not be of public health importance if the disease is very rare. The risk difference, on the other hand, measures direct health burden and the need for health services. Those who ate eclairs had a high chance (55%) of getting symptoms. A reduction of 51% substantially reduces the burden of the sport game attendants and the hospital services.

Attributable fraction population indicates that the number of cases could have been reduced by 87% had the eclairs not been contaminated. This outbreak was transient if we compare it with a chronic overwhelming problem such as cardio-vascular disease or cancer. Even a relatively low level of fraction of risk attributable to tobacco in the population, say 20%, could lead to a huge amount of resources spent in health services.

Attributable fraction exposure has little to do with level of disease burden in the population. It is equal to 1 - RR^{-1}, and is therefore just another way to express the risk ratio.

We have eclair as a cause of disease. There are some interventions that can prevent the diseases such as vaccination, education, law enforcement and improvement of environment. In our example, let's assume that not eating eclairs is a prevention process.

```
> eclair.no <- !eclair.eat    # The ! sign means "NOT"
> cs(case, eclair.no)
       eclair.no
case    FALSE TRUE Total
  FALSE 300   279  579
  TRUE  383   15   398
  Total 683   294  977

        Rne   Re   Rt
  Risk  0.56  0.05 0.41
                                   Estimate Lower95  Upper95
 Risk difference (absolute change) -0.51    -0.44    -0.58
 Risk ratio                         0.09     0.12     0.07
 protective efficacy (%)            90.9
 Number needed to treat (NNT)       1.96
```

The risk among the exposed (not eating eclair) is lower than that among the non-exposed (eating eclair). The risk difference changes sign to negative. The risk ratio reciprocates to a small value of 0.09. Instead of displaying the attributable fraction exposure and attributable fraction population, the command shows protective efficacy and number needed to treat (NNT).

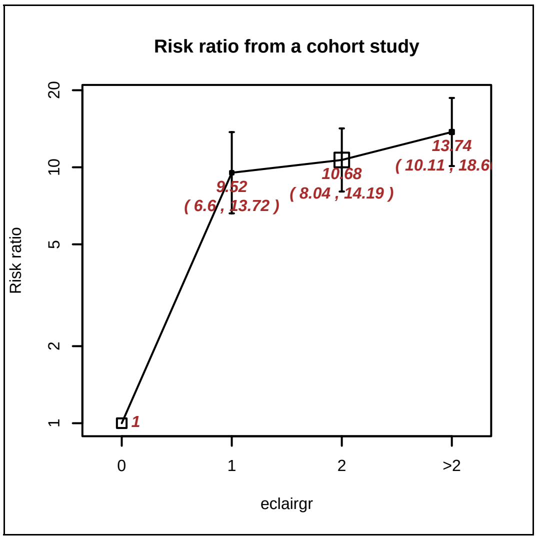
From the protective efficacy value, the exposure to the prevention program would have reduced the risk of the eclair eater (unexposed under this hypothetical condition) by 90.9%. NNT is just the reciprocal of the negative of risk difference. A reduction of risk of 0.51 comes from an intervention on one individual. A reduction of 1 would need to come from an intervention on 1/0.51 or 1.96 individuals. An intervention of high NNT would need to be given to many individuals just to avert one unwanted event. The lowest possible level of NNT is 1 or perfect prevention which also has 100% protective efficacy. NNT is a part of measurement of worthiness of intervention (either prevention or treatment) technology. To avert the same type of unwanted event, an intervention with low NNT is preferred to another with high NNT, although the cost must also be taken into account.

Dose-response relationship

One of the criteria for causation is the evidence of a dose-response relationship. If a higher dose of exposure is associated with a higher level of risk in a linear fashion, then the exposure is likely to be the cause.

We now explore the relationship between the risk of getting the disease and the number of eclairs consumed.

```
> cs(case, eclairgr)
                eclairgr
case             0    1     2     >2
  FALSE          279  54    203   38
  TRUE           15   51    243   89

  Absolute risk  0.05 0.49  0.54  0.7
  Risk ratio     1    9.52  10.68 13.74
  lower 95% CI        6.6   8.04  10.11
  upper 95% CI        13.72 14.19 18.66

Chi-squared = 237.12 , 3 d.f., P value = 0
Fisher's exact test (2-sided) P value = 0
```



The risk ratio increases as the dose of exposure to eclairs increases. The step from not eating to the first group (up to one piece) is wide whereas further increases are shown at a flatter slope. The P values in the output are both zero. In fact, they are not really zero, but have been rounded to three decimal places. The default rounding of decimals of odds ratios and relative risks is two and for the P values is three. See the help page for more details on the arguments.

Before finishing this chapter, the current data is saved for further use.

```
> save(.data, file = "Chapter8.Rdata")
```

Exercise

Compute the attributable risk and risk ratio of 'beefcurry', 'saltegg' and 'water'. Are these statistically significant? If so, what are the possible reasons?

Chapter 9: Odds Ratios, Confounding and Interaction

Having assessed various parameters of risk of participants in the outbreak in the last chapter, we now focus on confounding among various types of foods.

The assessment of risk in this chapter is changed from the possible cause. The next step in analysing the outbreak is to deal with the level of risk. Let's first load the data saved from the preceding chapter.

```
> zap()
> load("Chapter8.Rdata")
> use(.data)
```

Odds and odds ratio

Odds has a meaning related with probability. If *p* is the probability, *p*/(1-*p*) is known as the odds. Conversely, the probability would be equal to odds/(odds+1).

```
> tab1(case)
        Frequency Percent
FALSE         625    57.1
TRUE          469    42.9
  Total      1094   100.0
```

The probability of being a case is 469/1094 or 42.9%. In this situation where non-cases are coded as 0 and cases as 1, the probability is

```
> mean(case)
```

On the other hand the odds of being a case is 469/625 = 0.7504, or

```
> mean(case)/(1 - mean(case))
```

Note that when there are missing values in the variable, the `mean` function must have the argument 'na.rm' set to TRUE. For example the odds of eating eclairs is:

```
> m.eclair <- mean(eclair.eat, na.rm = TRUE)
> m.eclair /(1 - m.eclair)
[1] 2.323129
```

While a probability always ranges from 0 to 1, an odds ranges from 0 to infinity. For a cohort study we may compute the ratios of the odds of being a case among the exposed vs the odds among the non-exposed.

```
> table(case, eclair.eat)
       eclair.eat
case    FALSE TRUE
  FALSE   279  300
  TRUE     15  383
```

The conventional method for computing the odds ratio is therefore:

```
> (383/300)/(15/279)
[1] 23.746
```

This is the same value as the ratio of the odds of being exposed among cases and among non-cases.

```
> (383/15)/(300/279)
```

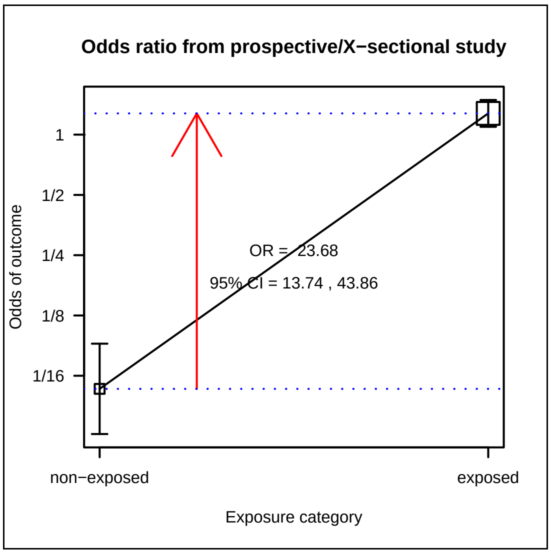
It is also equal to the ratio between the cross-product.

```
> (383 * 279)/(300 * 15)
```

Epicalc has a function *cc* producing odds ratio, its 95% confidence interval, performing the chi-squared and Fisher's exact tests and drawing a graph for the explanation.

```
> cc(case, eclair.eat)
       eating eclair
case    FALSE TRUE Total
  FALSE   279  300   579
  TRUE     15  383   398
  Total   294  683   977
OR =  23.68
95% CI = 13.74 43.86
Chi-squared = 221.21 ,  1 d.f. , P value = 0
Fisher's exact test (2-sided) P value = 0
```

The value of odds ratio from the *cc* function is slightly different from the calculations that we have done. This is because the *cc* function uses the exact method to calculate the odds ratio.



The vertical lines of the resulting graph show the estimate and 95% confidence intervals of the two odds of being diseased, non-exposed on the left and exposed on the right, computed by the conventional method. The size of the box at the estimate reflects the relative sample size of each subgroup. There were more exposed than non-exposed. The non-exposed group has the estimate value slightly below 1/16 since the real value is 15/279. The exposed group estimate is 383/300 or slightly higher than 1. The latter value is over 23 times of the former.

```
> fisher.test(table(case, eclair.eat))$estimate
odds ratio
  23.681

> fisher.test(table(case, eclair.eat))$conf.int
[1] 13.736 43.862
attr(,"conf.level")
[1] 0.95
```

Confounding and its mechanism

For 'saltegg', the odds ratio can be similarly computed.

```
> cc(case, saltegg)
       saltegg
case     0    1 Total
  FALSE 66  554   620
  TRUE  21  448   469
  Total 87 1002  1089
OR =  2.54
95% CI = 1.51 4.44
Chi-squared = 13.82 ,  1 d.f. , P value = 0
Fisher's exact test (2-sided) P value = 0
```

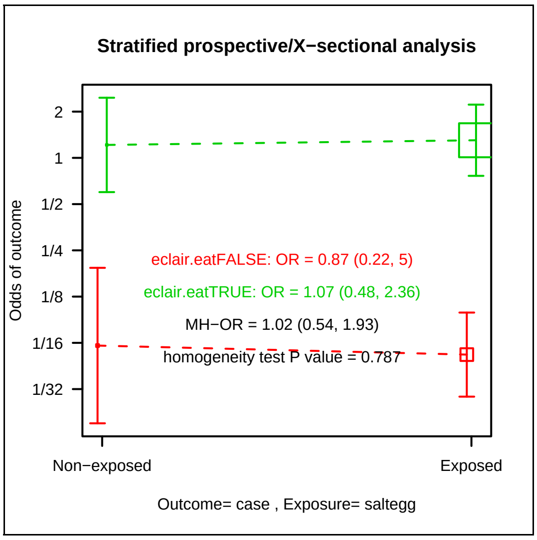
The total valid records for computation is 1,089, which is higher than 977 of the cross-tabulation results between 'case' and 'eclair.eat'. The value of the odds ratio is not as high but is of statistical significance. Similar to the analysis of the odds ratio for 'eclair', the size of the box on the right is much larger than that on the left indicating a large proportion of exposure.

Both eclairs and salted eggs have significant odds ratios and were consumed by a large proportion of participants. Let's check the association between these two variables.

```
> cc(saltegg, eclair.eat, graph = FALSE)
       eating eclair
saltegg FALSE TRUE Total
  0        53   31    84
  1       241  647   888
  Total   294  678   972
OR =  4.58
95% CI = 2.81 7.58
Chi-squared = 47.02 ,  1 d.f. , P value = 0
Fisher's exact test (2-sided) P value = 0
```

There might be only one real cause and the other was just confounded. In other words, those participants who ate salted eggs also tended to eat eclairs. Stratified analysis gives the details of confounding as follows.

```
> mhor(case, saltegg, eclair.eat)
```



```
Stratified analysis by  eclair.eat
                     OR lower lim. upper lim. P value
eclair.eat FALSE  0.874      0.224       5.00   0.739
eclair.eat TRUE   1.073      0.481       2.36   0.855
M-H combined      1.023      0.541       1.93   0.944
M-H Chi2(1) = 0 , P value = 0.944
Homogeneity test, chi-squared 1 d.f.=0.07, P value = 0.787
```

The above analysis of association between the disease and salted egg is stratified by level of eclair consumption based on records that have valid values of 'case', 'eclair.eat' and 'saltegg'. There are two main parts of the results. The first part concerns the odds ratio of the exposure of interest in each stratum defined by the third variable, in this case 'eclair.eat' as well as the odds ratio and chi-squared statistics computed by Mantel-Haenszel's technique. The second part suggests whether the odds ratio of these strata can be combined. We will focus on the first part at this stage and come back to the second part later.

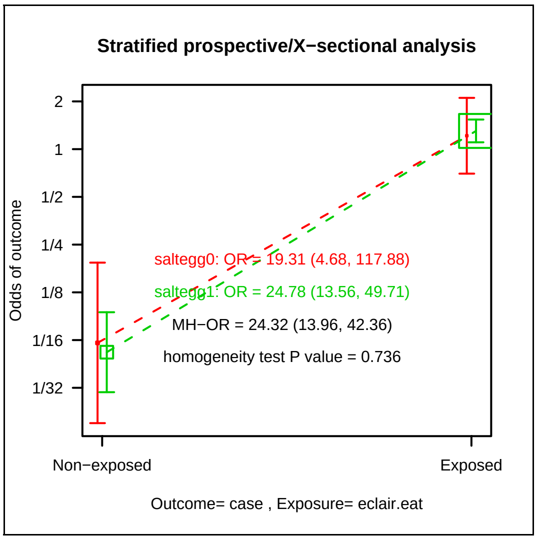
In both strata, the odds ratios are close to 1 and are not statistically significant. The slopes of the two lines are rather flat. The Mantel-Haenszel (MH) odds ratio, also called the *adjusted* odds ratio, is the weighted average of the two odds ratios, which is also close to 1. Both the stratum-specific odds ratios and the MH odds ratio are not significantly different from 1 but the crude odds ratio is significantly different. The distortion of the crude result from the adjusted result is called confounding.

The mechanism of this confounding can be explained with the above graph. The upper line of the graph denotes the subset or stratum of subjects who had eaten eclairs whereas the lower line represents those who had not. The upper line lies far above the lower line meaning that the subset of eclair eaters had a much higher risk than the non-eaters. The distance between the two lines is between 16 to 32 fold of odds. It is important to note that the distribution of subjects in this study is imbalanced in relation to eclair and salted eggs consumption. On the right-hand side (salted egg consumers), there are alot more eclair eaters (upper box) than non-eaters (lower box). The centre of this right-hand side then tends to be closer to the location of the upper box. In contrast, on the left-hand side, or those not consuming salted eggs, the number of eclair non-consumers (as represented by the size of the lower box) is higher than that of the consumers. The centre of the left-hand side therefore tends to lie closer to the lower box. In other words, when the two strata are combined, the (weighted average) odds of diseased among the salted egg consumers is therefore closer to the upper box. The opposite is true for the left-hand side where the weighted average odds of getting the disease should be closer to the lower box. A higher average odds on the right-hand side leads to the crude odds ratio being higher than one. This crude odds ratio misleads us into thinking that salted egg is another cause of the disease where in fact it was just confounded by eclairs. The level of confounding is noteworthy only if both of the following two conditions are met.

Firstly, the stratification factor must be an independent risk factor. Secondly, there must be a significant association between the stratification factor and the exposure of interest.

Now we check whether the relationship between the disease and eclair is confounded by salted egg.

```
> mhor(case, eclair.eat, saltegg)
Stratified analysis by  saltegg
               OR lower lim. upper lim.  P value
saltegg 0    19.3       4.68      117.9 6.06e-07
saltegg 1    24.8      13.56       49.7 2.42e-51
M-H combined 24.3      13.96       42.4 8.12e-49
M-H Chi2(1) = 215.63 , P value = 0
Homogeneity test, chi-squared 1 d.f. = 0.11 , P value = 0.736
```



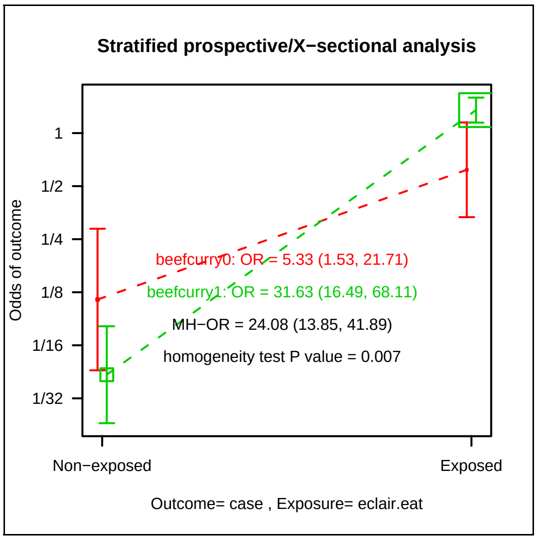
Stratified by 'saltegg', the odds ratio of eclair.eat in both strata (19.3 and 24.8) and the MH odds ratio (24.3) are strong and close to the crude odds ratio (23.68).

Graphically, the two lines of strata are very close together indicating that 'saltegg' is not an independent risk factor. In each of the exposed and non-exposed groups, the odds for disease are close and the weighted average odds is therefore not influenced by the number of subjects. Thus not being an independent risk factor, a variable cannot confound another exposure variable.

Interaction and effect modification

Let's analyse the association between eating eclairs and the developing acute gastrointestinal illness again but now using 'beefcurry' as the stratification factor.

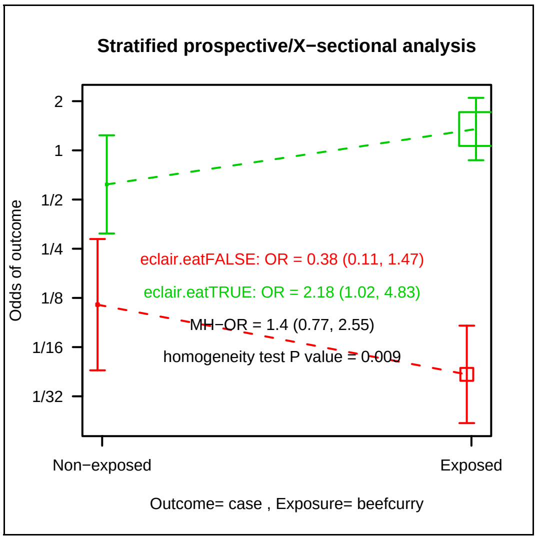
```
> mhor(case, eclair.eat, beefcurry)
Stratified analysis by  beefcurry
                OR lower lim. upper lim.  P value
beefcurry 0   5.33       1.53       21.7 3.12e-03
beefcurry 1  31.63      16.49       68.1 4.79e-56
M-H combined 24.08      13.85       41.9 1.39e-48
M-H Chi2(1) = 214.56 , P value = 0
Homogeneity test, chi-squared 1 d.f. = 7.23 , P value = 0.007
```



The slopes of the odds ratios of the two strata cross each other. Among those who had not eaten beef curry, the odds of getting the disease among those not eating eclair was slightly below 1 in 6. The odds increases to over 1 in 2 for those who ate eclairs only. This increase is 5.33 fold or an odds ratio of 5.33. In contrast, the baseline odds among those eating beef curry only (left point of the green line) is somewhere between 1 in 32 and 1 in 16, which is the lowest risk group in the graph. The odds however steps up very sharply to over 1 among the subjects who had eaten both eclairs and beef curry. The homogeneity test in the last line concludes that the odds ratios are not homogeneous. In statistics, this is called significant interaction. In epidemiology, the effect of 'eclair' was modified by 'beefcurry'. Eating beef curry increased the harmful effect of eclair or increased the susceptibility of the person to get ill by eating eclairs.

We now check the effect of 'beefcurry' stratified by 'eclair.eat'.

```
> mhor(case, beefcurry, eclair.eat)
Stratified analysis by  eclair.eat
                    OR lower lim. upper lim. P value
eclair.eat FALSE 0.376      0.111       1.47  0.1446
eclair.eat TRUE  2.179      1.021       4.83  0.0329
M-H combined     1.401      0.769       2.55  0.2396
M-H Chi2(1) = 1.38 , P value = 0.24
Homogeneity test, chi-squared 1 d.f. = 6.78 , P value = 0.009
```



The effect of beef curry among those not eating eclairs tends to be protective but without statistical significance. The odds ratio among those eating eclairs is 2.18 with statistical significance. The homogeneity test also concludes that the two odds ratios are not homogeneous. The stratification factor eclair has modified the effect of beef curry from a non-significant protective factor to a significant risk factor.

Tabulation and stratified graphs are very useful in explaining confounding and interaction. However, they are limited to only two or three variables. For a dataset with a larger number of variables, logistic regression is needed. We put the new variable 'eclair.eat' into **`.data`** by using *`label.var`* and save the whole data frame for future use with logistic regression.

```
> label.var(eclair.eat, "ate at least some eclair")
> save(.data, file="chapter9.Rdata")
```

Exercise

Analyse the effect of drinking water on the odds of the disease. Check whether it is confounded with eating eclairs or other foods. Check for interaction.

Chapter 10: Basic Data Management

Data cleaning

The previous datasets were relatively clean. Let's look at an uncleaned dataset that came from a family planning clinic in the mid 1980's. The coding scheme can be seen from

```
> help(Planning)
```

Cleaning will enable you to learn *Epicalc* functions for data management.

```
> zap()
> data(Planning)
> des(Planning)
```

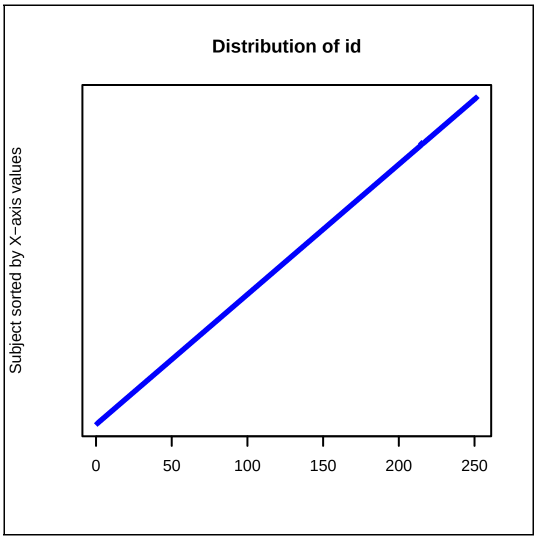
Note that all of the variable names are in upper case. To convert them to lower case simply type the following command.

```
> names(Planning) <- tolower(names(Planning))
> use(Planning)
> summ()

No. of observations = 251

   Var. name Obs.  mean   median  s.d.   min.   max.
1  id        251   126    126     72.6   1      251
2  age       251   27.41  27      4.77   18     41
3  relig     251   1.14   1       0.59   1      9
4  ped       251   3.83   3       2.32   0      9
5  income    251   2.84   2       2.38   1      9
6  am        251   20.66  20      5.83   15     99
7  reason    251   1.55   1       0.86   1      9
8  bps       251   137.74 110     146.84 0      999
9  bpd       251   97.58  70      153.36 0      999
10 wt        251   52.85  51.9    11.09  0      99.9
11 ht        251   171.49 154     121.82 0      999
```

Identifying duplication ID

Let's look more closely at the 'id' object. This variable represents the unique identification number for the subject.

```
> summ(id)
  Valid obs. mean    median  s.d.   min.   max.
  251        125.996 126     72.597 1      251
```



The graph looks quite uniformly distributed. However, the mean of id (125.996) is not equal to what it should be.

```
> mean(1:251)
[1] 126
```

There must be some duplication and/or some gaps within these id numbers. Looking carefully at the graph, there is no noticeable irregularity.

To check for duplication, we can type the following:

```
> any(duplicated(id))
[1] TRUE
```

The result tells us that there is in fact at least one duplicated id. To specify the id of the duplicates type:

```
> id[duplicated(id)]
[1] 215
```

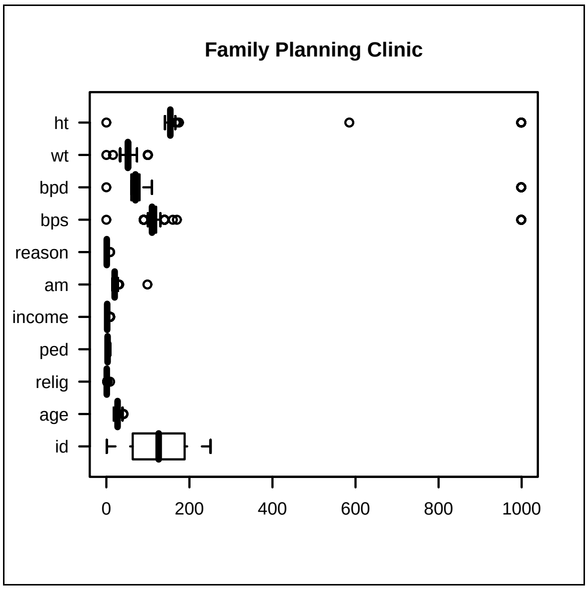
We see that id = 215 has one duplicate. Further inspection of the data reveals that the record numbers are 215 and 216. These two records should be investigated as to which one is incorrect. One of them should be changed to 'id' = 216.

Missing values

This file is not ready for analysis yet. As is often the case, the data were coded using outlier numbers to represent missing codes.

We first explore the data with boxplots.

```
> boxplot(.data, horizontal=T, las=1, main="Family Planning
  Clinic")
```



The outlier values of 'bps', 'bpd' and 'ht' are rather obvious. These are confirmed with the numerical statistics from the *summ* command seen earlier in this chapter.

In this dataset, the value '9' represents a missing code for religion (3rd variable), patient education (4th variable), income group (5th variable) and reason for family planning (7th variable).

There are four methods of changing values to missing (NA). The first method is based on the function `replace`, which handles one vector or variable at a time. The second uses extraction and indexing with subscript '`[]`'. This method can handle either a vector or array (several variables at the same time). The third method is based on the `transform` command. These three methods use commands that are native to **R**. The fourth method uses the *recode* command from *Epicalc*, which is by far the simplest method.

We will use the `replace` function for the 3rd variable, 'relig', extraction and indexing for the 4th to 7th variables, 'ped', 'am', 'income' and 'reason', `transform` for the 'wt' variable, and finally *`recode`* for the remaining necessary variables.

Replacing values in a data frame

We wish to replace all occurrences of 9 with the missing value 'NA'. The replace function handles only one variable at a time.

```
> summ(relig)
```

We wish to replace all occurrences of 9 with the missing value 'NA'.

```
> replace(relig, relig==9, NA) -> .data$relig
```

There are three essential arguments to the `replace` function; the target vector, the index vector and the value. See the online help for more detailed information on its usage.

The first argument, '`relig`', is the target vector containing values to be replaced. The second argument, '`relig==9`', is the index vector specifying the condition, in this case, whenever '`relig`' is equal to 9. The final argument, 'NA', is the new value that will replace the old value of 9. Thus, whenever '`relig`' is equal to 9, it will be replaced with 'NA'.

Note that the index vector, or condition for change, need not be the same vector as the target vector. For example, one may want to coerce the value of diastolic blood pressure to be missing if the systolic blood pressure is missing.

Secondly, `replace` is a function, not a command. It has no effect on the original values. The values obtained from this function must be assigned to the original values using the assignment operators, '`->`' or '`<-`'.

Right now, the variable has changed.

```
> summ(.data$relig)
  Obs.  mean   median  s.d.   min.   max.
  250   1.108  1       0.31   1      2
```

There was one subject with a missing value leaving 250 records for statistical calculations. The remaining subjects have values of one and two only for 'religion'.

Changing values with extraction and indexing

The first variable to be replaced with this method is the 6th one, 'am', which denotes age at first marriage.

```
> summ(.data$am)
  Valid obs. mean   median  s.d.   min.   max.
  251        20.657 20      5.83   15     99
```

The value 99 represents a missing value code during data entry. Note that the mean, median and standard deviation are not correct due to this coding of missing values. Instead of using the previous method, the alternative is:

```
> .data$am[.data$am==99] <- NA
```

With the same three components of the target vector, conditions and replacing value, this latter command is slightly more straightforward than the above one using the `replace` function.

This method can also be used for many variables with the same missing code. For example, the 4th, 5th and 7th variables all use the value 9 as the code for a missing value.

```
> .data[,c(4,5,7)][.data[,c(4,5,7)]==9] <- NA
```

All the 4th, 5th, and 7th variables of **`.data`** that have a value of 9 are replaced with 'NA'. The above command can be explained as follows. There are two layers of subsets of **`.data`** marked by '[ ]'.

`'.data[,c(4,5,7)]'` means extract all rows of columns 4, 5 and 7, ('ped', 'income' and 'reason').

`'[.data[,c(4,5,7)]==9]'` means the subset of each particular column where the row is equal to 9.

'`<- NA`' means the epression on the left is to be assigned a missing value (NA).

Thus, for these four variables, any element in which the value equals 9 will be replaced by NA.

Transforming variables in a data frame

The function `transform` does a similar job as the previous methods described above. For example, to transform 'wt'

```
> transform(.data, wt=ifelse(wt>99, NA, wt)) -> .data
```

The expression inside the function tells **R** to replace values of 'wt' that are greater than 99 with the NA value. The resulting object is saved into the data frame.

Now check the 'wt' variable inside the data frame.

```
> summ(.data$wt)
  Valid obs. mean   median  s.d.   min.   max.
  246        51.895 51.45   8.91   0      73.8
```

Note the two outliers on the left-hand side of the graph. Similar to the results of previous methods, `transform` did not change the 'wt' variable inside the data frame in the search path.

```
> summ(wt)
  Valid obs. mean   median  s.d.   min.   max.
  251        52.851 51.9    11.09  0      99.9
```

Note that the transformed data frame does not keep the variable labels or descriptions with it. The new **`.data`** will have all variable descriptions removed. So this method reduces the power of *Epicalc*.

Recoding values using Epicalc

The function *`recode`* in *Epicalc* was created to make data transformation easier. Similar to other commands in *Epicalc*, for example *`use`*, *`des`*, *`summ`*, *`tab1`* and *`label.var`*, the command *`recode`* is restricted to the setting of having **`.data`** as the default data frame.

We require replacing the values '999' to a missing value for variables 'bps', 'bpd' and 'ht'. The command is simple. Let's start with 'bps'.

```
> recode(var=bps, old.value=999, new.value=NA)
> summ(.data)
```

Notice that the variable 'bps' has been changed. In fact, *`recode`* has automatically detached the old data frame and attached to the new one, as shown below.

```
> summ(bps)
  Valid obs. mean    median  s.d.   min.   max.
  244        113.033 110     14.22  0      170
```

Variable 'bps' in **`.data`** and that in the search path have been synchronised. The number of valid records is reduced to 244 and the maximum is now 170 not 999. This automatic updating has also affected other variables in the search path that we changed before.

```
> summ(am)
  Valid obs. mean   median  s.d.   min.   max.
  250        20.344 20      3.06   15     31
```

When the variable 'am' is used as the argument of *`summ`*, the program looks for an independent object called 'am', which does not exist. It then looks in the search path. Since the data frame in the search path ('search()[2]') has been updated with the new **`.data`**, the variable 'am' that is used now is the updated one which has been changed from the command in the preceding section. The command *`recode`* makes variable manipulation simpler than the above three standard **R** methods.

The command *recode* can be further simplified:

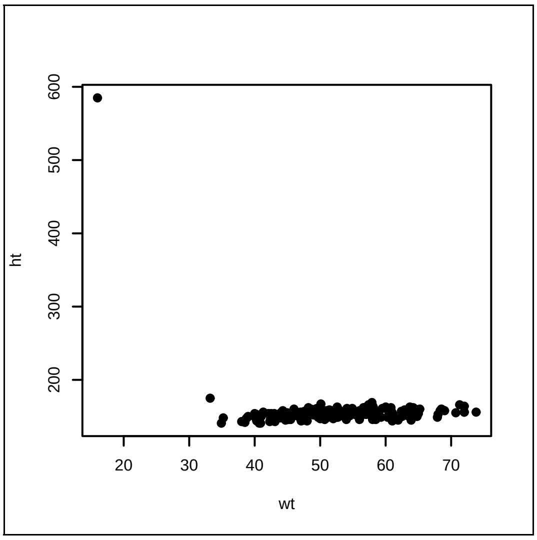
```
> recode(bpd, 999, NA)
> recode(ht, 999, NA)
> summ()
```

All the maxima have been corrected but the minima of 0 are also missing values for the last four variables plus 'ped'. We can use *recode* to turn all the zeros into missing values in one step.

```
> recode(c(ped, bps, bpd, wt, ht), 0, NA)
> summ()
No. of observations = 251
   Var. name Obs.  mean   median  s.d.   min.  max.
============ variables #1, #2, #3 omitted =========
4  ped       226   3.3    2       1.66   2     7
============ variables #5, #6, #7 omitted =========
8  bps       243   113.5  110     12.25  90    170
9  bpd       243   72.02  70      9.9    60    110
10 wt        245   52.11  51.5    8.28   16    73.8
11 ht        245   155.3  153     28.08  141   585
```

The minimum weight of 16kg and the maximum height of 585cm are dubious and in fact should not be accepted. Any weight below 30kg and any height above 200cm should also be treated as missing (unless there are very good reasons to leave them as is). A scatter plot is also useful here.

```
> plot(wt, ht, pch=19)
```

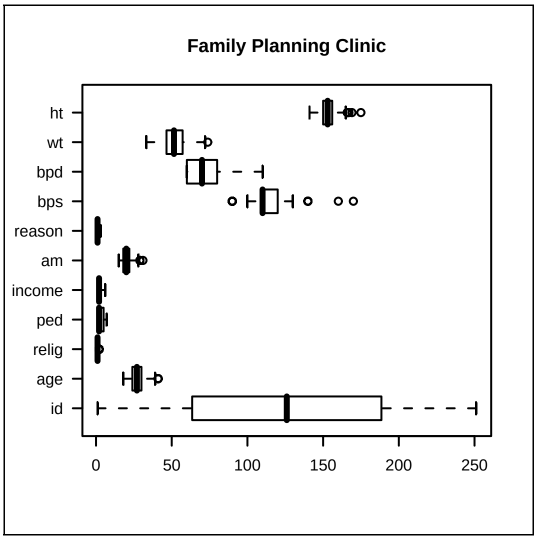


The outlier is clearly seen (top left corner). To correct these errors type:

```
> recode(wt, wt < 30, NA)
> recode(ht, ht > 200, NA)
> summ()
```

It should be noted that after cleaning, the effective sample size is somewhat less than the original value of 251. The box plot of all variables now has a different appearance.

```
> boxplot(.data, horizontal=T, main="Family Planning Clinic",
  las=1)
```



Labelling variables with 'label.var'

When there are only a few variables in the dataset, all of which are for common purposes, such as 'age', 'sex', or 'education', naming is not a problem. However, when there are a large number of variables, it is difficult to have intuitively understandable names for each variable. A system separating variable labels from variable names is a better way of documentation.

R does not come with a built-in variable labelling facility. *Epicalc* however, adds in this useful facility in a simple way.

Firstly, the variable names of the data are displayed.

```
> names(.data)
[1] "id"     "age"    "relig"  "ped"   "income" "am"
[7] "reason" "bps"     "bpd"    "wt"    "ht"
```

Then, an appropriate label or description for each variable can be created one at a time.

```
> label.var(id, "Id code")
```

At this stage, checking description of the dataset will reveal the description of the first variable.

```
> des()
No. of observations =251
   Variable      Class           Description
1  id            numeric         Id code
2  age           numeric
3  relig         numeric
========= subsequent lines omitted ==========
```

A description of the variable alone can also be displayed.

```
> des(id)

'id' is a variable found in the following source(s):

 Var. source  Var. order Class   # records Description
 .data        1          numeric 251
```

Now let's complete all other variable labels.

```
> label.var(age, "age")
> label.var(relig, "religion")
> label.var(ped, "eduction")
> label.var(income, "monthly income")
> label.var(am, "age(yr) 1st marriage")
> label.var(reason, "reason for fam. plan.")
> label.var(bps, "systolic BP")
> label.var(bpd, "diastolic BP")
> label.var(wt, "weight (kg)")
> label.var(ht, "height (cm)")
> des()

No. of observations =251
   Variable     Class          Description
1  id           numeric        ID code
2  age          numeric        age
3  relig        numeric        religion
4  ped          numeric        eduction
5  income       numeric        monthly income
6  am           numeric        age(yr) 1st marriage
7  reason       numeric        reason for fam. plan.
8  bps          numeric        systolic BP
9  bpd          numeric        diastolic BP
10 wt           numeric        weight (kg)
11 ht           numeric        height (cm)
```

It is advised to keep each label short since it will be frequently used in the process of automatic graphical display and tabulation.

Labelling a categorical variable

Labelling values of a categorical variable is a good practice. It is a part of important documentation. During the analysis, a labelled variable is much easier to understand and interpret than an unlabelled one.

As mentioned previously, the best way to label variables is during the preparation of data entry using the data entry software. However, occasionally one may encounter an unlabelled dataset, such as those directly imported from EpiInfo, 'txt' or 'csv' formats. It is therefore important to know how to label variables in **R**.

In our example of the family planning data the variable 'ped' (patient's education level) is an unlabelled categorical variable. In fact, at this stage, it is not really a categorical variable. When we summarise the statistics, either by the `summary(.data)` command or by *`summ`*, both outputs show means, medians and standard deviations, indicating a continuous, numeric variable.

```
> summary(ped)
   Min. 1st Qu. Median  Mean 3rd Qu.   Max.    NA's
  2.000   2.000  2.000  3.296  5.000  7.000  25.000

> summ(ped)
  Obs.  mean   median  s.d.   min.   max.
  226   3.296  2       1.66   2      7
```

Note that there is no count for category 1 of 'ped'. According to the coding scheme:

1 = no education, 2 = primary school, 3 = secondary school, 4 = high school,
5 = vocational school, 6 = bachelor degree, 7 = other.

The data are numeric and therefore need to be converted into a factor. The labels can be put into a list of 7 elements.

```
> label.ped <- list(None="1", Primary="2", "Secondary
  school"="3", "High school"="4", Vocational="5", "Bachelor
  degree"="6", Others="7")
```

Each label needs to be enclosed in double quotes if it contains a space, otherwise it is optional. For example, one can have: `None="1" or "None"="1"`.

To convert a numeric vector to a categorical one use the '`factor`' function.

```
> educ <- factor(ped, exclude = NULL)
```

The new variable is a result of *factoring* the values of 'ped' in **`.data`**. The argument 'exclude' is set to 'NULL' indicating no category (even missing or 'NA') will be excluded in the factoring process.

```
> summary(educ)
   2    3    4    5    6    7 <NA>
 117   31   20   26   16   16   25
```

We can check the labels of a factor object using the levels command.

```
> levels(educ)
[1] "2" "3" "4" "5" "6" "7" NA
```

There are seven known levels, ranging from "2" to "7" and one missing level (NA). Note that these numbers are actually characters or group names. There was no "1" in the data and correspondingly is omitted in the levels.

The *levels* for the codes should be changed to meaningful words as defined previouisly.

```
> levels(educ) <- label.ped
> levels(educ)
[1] "None"             "Primary"          "Secondary school"
[4] "High school"      "Vocational"       "Bachelor degree"
[7] "Others"
```

Adding a variable to a data frame

Note that the variable 'educ' is not inside the data frame **`.data`**. Remember that **R** has the capacity to handle more than one object simultaneously. However, although it is possible to go on analysing data with this variable outside the data frame, incorporating all the important variables into the main data frame **`.data`** is advised, especially if any sorting is done. In addition, the variable can have a descriptive label. More importantly, when necessary, the whole data frame including the old and new variables can be written into another data format easily (see the function 'write.foreign' in the foreign package).

```
> des() # same as before
```

To incorporate a new variable derived from the data frame **`.data`**, simply label the variable name as follows.

```
> label.var(educ, "education")
```

Then recheck.

```
> des()
No. of observations =251
   Variable      Class           Description
1  id            numeric         ID code
============ Variables # 2 to 11 omitted =======
12 educ          factor          education
```

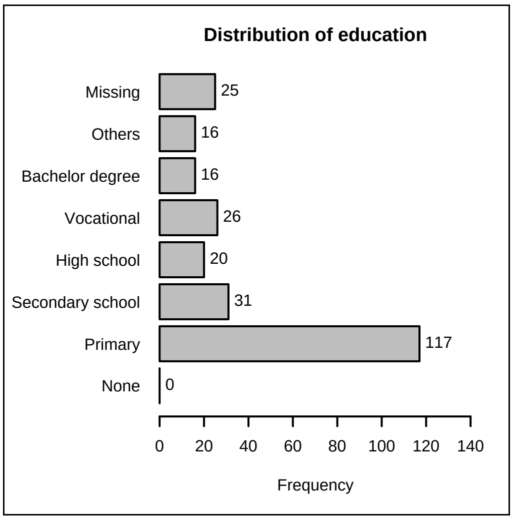
For a variable outside **`.data`**, the command *`label.var`* actually accomplishes five tasks.

- The new variable is incorporated into the data frame **`.data`**,
- The new variable is labelled with a description,
- The old data frame is detached,
- The old 'free' variable outside the data frame is removed, unless the argument 'pack=FALSE' is specified,
- The new data frame is attached to the search path.

Order of one-way tabulation

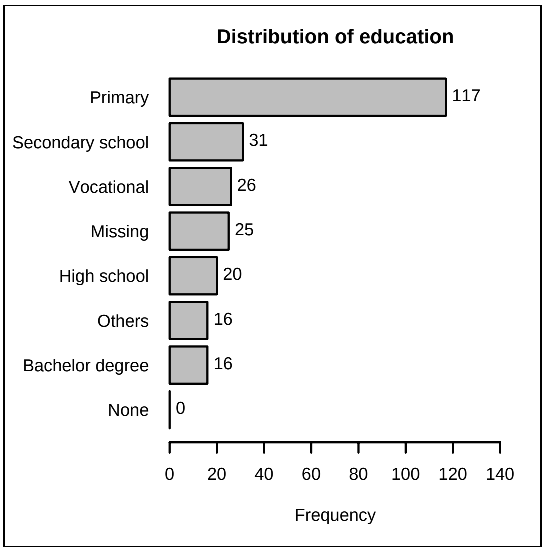
The new education variable can be tabulated.

```
> tab1(educ)
educ: education
                Frequency   %(NA+)   %(NA-)
None                    0      0.0      0.0
Primary               117     46.6     51.8
Secondary school       31     12.4     13.7
High school            20      8.0      8.8
Vocational             26     10.4     11.5
Bachelor degree        16      6.4      7.1
Others                 16      6.4      7.1
NA's                   25     10.0      0.0
   Total              251    100.0    100.0
```



The table and the graph show that most subjects had only primary education. A horizontal bar chart is produced when the number of groups exceeds 6 and the longest label of the group has more than 8 characters. The tabulation can also be sorted.

```
> tab1(educ, sort.group = "decreasing")
educ : education
                Frequency   %(NA+)   %(NA-)
Primary               117     46.6     51.8
Secondary school       31     12.4     13.7
Vocational             26     10.4     11.5
NA's                   25     10.0      0.0
High school            20      8.0      8.8
Bachelor degree        16      6.4      7.1
Others                 16      6.4      7.1
None                    0      0.0      0.0
  Total               251    100.0    100.0
```



Alternatively the sorting can be increasing.

```
> tab1(educ, sort.group = "increasing")
educ : education
                 Frequency   %(NA+)   %(NA-)
None                     0      0.0      0.0
Bachelor degree         16      6.4      7.1
Others                  16      6.4      7.1
High school             20      8.0      8.8
NA's                    25     10.0      0.0
Vocational              26     10.4     11.5
Secondary school        31     12.4     13.7
Primary                117     46.6     51.8
  Total                251    100.0    100.0
```

A sorted table and bar chart are easier to read and viewed when there is no order of category. However, education level is partially ordered in nature, so the non-sorted chart may be better.

Collapsing categories

Sometimes a categorical variable may have too many levels. The analyst may want to combine two or more categories together into one. For example, vocational and bachelor degree, which are the 5th and the 6th levels, could be combined into one level called 'tertiary'. We can do this by creating a new variable, which is then incorporated into **`.data`** at the end.

```
> ped2 <- educ
> levels(ped2)[5:6] <- "Tertiary"
> label.var(ped2, "level of education")
> des()
> tab1(ped2)

ped2 : level of education

                 Frequency   %(NA+)   %(NA-)
None                     0      0.0      0.0
Primary                117     46.6     51.8
Secondary school        31     12.4     13.7
High school             20      8.0      8.8
Tertiary                42     16.7     18.6
Others                  16      6.4      7.1
NA's                    25     10.0      0.0
  Total                251    100.0    100.0
```

The two categories have been combined into one giving 42 subjects having a tertiary level of education.

Conclusion

In this chapter, we have looked at a dataset with a lot of data cleaning required. In real practice, it is very important to have preventive measures to minimise any errors during data collection and data entry. For example, a constraint of range check is necessary in data entry. Missing values would better be entered with missing codes specific for the software. In EpiInfo, Stata and SPSS these are period marks '.' or simply left blank.

One of the best ways of entering data is to use the EpiData software, which can set legal ranges and several other logical checks as well as label the variables and values in an easy way. If this had been properly done, then the difficult commands used in this chapter would not have been necessary. In the remaining chapters, we will use datasets which have been properly entered, treated for missing values and properly labelled.

Whenever a variable is modified it is a good practice to update the variable inside the attached data frame with the one outside.

The best way to modify data is to use *recode*, which is a powerful command of Epicalc. It can work with one variable or a number of variables with the same recoding scheme or recoding a variable or variables under a condition. Finally, the best way to update the data frame with new or modified variable(s) is to use *label.var*. This command not only labels the variable for further use but also updates and incorporates the data frame with the variable outside. Attachment to the new data frame is automatic, making data manipulation in **R** more smooth and simple.

There are many other more advanced data management functions in **R** that are not covered in this chapter. These include aggregate, reshape and merge, and readers are encouraged to explore these very useful and powerful commands on their own.

Exercises

The **VCT** dataset contains data from a questionnaire involving female sex workers from Phuket, Thailand in 2004.

Read the file into **R** and use the commands in this chapter to clean the data.

Chapter 11: Scatter Plots & Linear Regression

Linear regression involves modelling a continuous outcome variable with one or more explanatory variables. With all data analysis the first step is always to explore the data. In this case, scatter plots are very useful in determining whether or not the relationships between the variables are linear.

Example: Hookworm & blood loss

The dataset in this chapter concerns the relationship between hookworm and blood loss from a study conducted in 1970.

```
> zap()
> data(Suwit); use(Suwit)
> des()

HW and Blood loss SEAJTMH 1970;
No. of observations = 15
  Variable      Class           Description
1 id            numeric
2 worm          numeric         No. of worms
3 bloss         numeric         Blood loss/day

> summm()

HW and Blood loss SEAJTMH 1970;
No. of observations =15

  Var. name Obs.  mean   median  s.d.   min.  max.
1 id        15    8      8       4.47   1     15
2 worm      15    552.4  525     513.9  32    1929
3 bloss     15    33.45  33.8    24.85  5.03  86.65
```

There are 3 variables and 15 records.

```
> .data
```

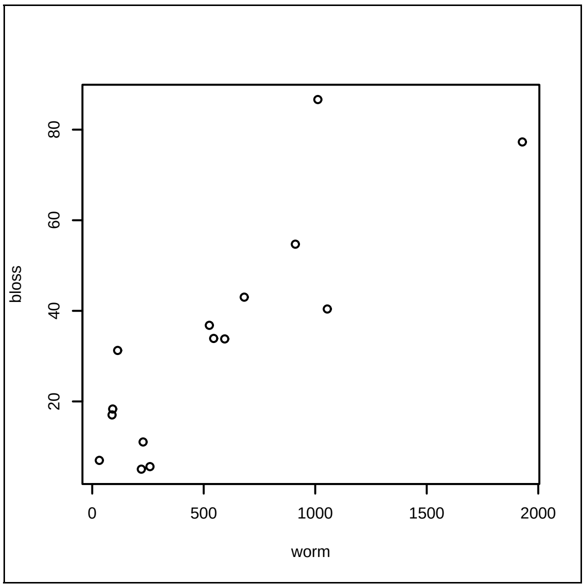
The file is clean and ready for analysis. With this small sample size it is somewhat straightforward to verify that there is no repetition of 'id' and no missing values. The records have been sorted in ascending order of 'worm' (number of worms) ranging from 32 in the first subject to 1,929 in the last one. Blood loss ('bloss') is however, not sorted. The 13th record has the highest blood loss of 86 ml per day, which is very high. The objective of this analysis is to examine the relationship between these two variables.

Scatter plots

When there are two continuous variables cross plotting is the first necessary step.

```
> plot(worm, bloss)
```

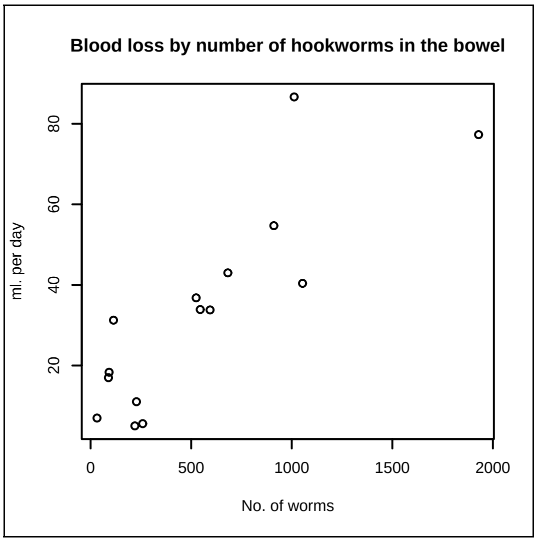
The above command gives a simple scatter plot with the first variable on the horizontal axis and the second on the vertical axis.



The names of the variables are used for the axis labels, and there is no title. The axis labels can be modified and a title added by supplying extra arguments to the plot function, as follows:

```
> plot(worm, bloss, xlab="No. of worms", ylab="ml. per day",
  main = "Blood loss by number of hookworms in the bowel")
```

For a small sample size, putting the identification of each dot can improve the information conveyed in the graph.

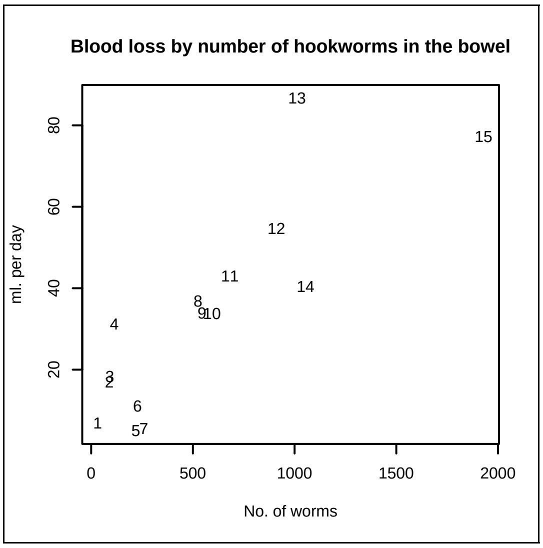


```
> plot(worm, bloss, xlab="No. of worms", ylab="ml. per day",
  main="Blood loss by number of hookworms in the bowel",
  type="n")
```

The above command produces an empty plot. The argument 'type' specifies the type of plot to be drawn. A value of "n" tells **R** not to plot anything. This is to set a proper frame for further points and lines.

The variable 'id' can be used as the text to write at the coordinates using the `text` command.

```
> text(worm, bloss, labels=id)
```



In order to draw a regression line, a linear model using the above two variables should be fit to the data.

Components of a linear model

The function `lm` is used to perform linear modelling in **R**.

```
> lm1 <- lm(bloss ~ worm)
> lm1
Call:
lm(formula = bloss ~ worm)
Coefficients:
(Intercept)         worm
   10.84733      0.04092
```

The model '`lm1`' is created. Be careful not to confuse the letter "`l`" with the number "`1`", which look very similar. Displaying the model by typing '`lm1`' gives limited information. To get more information, one can look at the attributes of this model, its summary and attributes of its summary.

```
> attr(lm1, "names")
 [1] "coefficients"  "residuals"     "effects"
 [4] "rank"          "fitted.values" "assign"
 [7] "qr"            "df.residual"   "xlevels"
[10] "call"          "terms"         "model"
```

There are 12 attributes. Most of them can be displayed with the `summary` function.

```
> summary(lm1)
```

```
  Call:
lm(formula = bloss ~ worm)

Residuals:
     Min       1Q   Median       3Q      Max
-15.8461 -10.8118   0.7502   4.3562  34.3896

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 10.84733    5.30857    2.04    0.062
worm         0.04092    0.00715    5.73    7e-05

Residual standard error: 13.7 on 13 degrees of freedom
Multiple R-Squared: 0.716,   Adjusted R-squared: 0.694
F-statistic: 32.8 on 1 and 13 DF,  p-value: 6.99e-05
```

The first section of summary shows the formula that was called. The second section gives the distribution of residuals. The pattern is clearly not symmetric. The maximum (34.38) is further away from zero compared to the minimum (-15.84) and the first quartile (-10.81) is further from the median (0.75) than the third quartile (4.35) is. Otherwise, the median is close to zero. The third section gives coefficients of the intercept and the effect of 'worm' on blood loss. The intercept is 10.8 meaning that when there are no worms, the blood loss is estimated to be 10.8 ml per day. This is however, not significantly different from zero as the P value is 0.0618. The coefficient of 'worm' is 0.04 indicating that each worm will cause an average of 0.04 ml of blood loss per day. Although the value is small, it is highly significantly different from zero. When there are many worms, the level of blood loss can be very substantial.

The multiple R-squared value of 0.716 indicates that 71.6% of the variation in the data is explained by the model. The adjusted value is 0.6942. (The calculation of R-squared is discussed in the analysis of variance section below). The last section describes more details of the residuals and hypothesis testing on the effect of 'worm' using the F-statistic. The P value from this section (6.99×10^{-5}) is equal to that tested by the t-distribution in the coefficient section. This F-test more commonly appears in the analysis of variance table.

Analysis of variance table, R-squared and adjusted R-squared

```
> summary(aov(lm1))
            Df Sum Sq Mean Sq F value   Pr(>F)
worm         1 6192     6 192    32.8    7e-05
Residuals   13 2455       189
```

The above analysis of variance (aov) table breaks down the degrees of freedom, sum of squares and mean square of the outcome (blood loss) by sources (in this case there only two: 'worm' and 'Residuals').

The so-called 'square' is actually the square of difference between the value and the mean. The total sum of squares of blood loss is therefore:

```
> SST <- sum((bloss-mean(bloss))^2); SST
[1] 8647
```

The sum of squares from residuals is:

```
> SSR <- sum(residuals(lm1)^2); SSR
[1] 2455.5  # See also the analysis of variance table
```

The sum of squares of worm or sum of squares of difference between the fitted values and the grand mean is:

```
> SSW <- sum((fitted(lm1)-mean(bloss))^2); SSW
[1] 6191.6
```

The latter two sums add up to the first one. The R-squared is the proportion of sum of squares of the fitted values to the total sum of squares.

```
> SSW/SST
[1] 0.71603
```

This value of R-squared can also be said to be the percent of reduction of total sum of squares when the explanatory variable is fitted. Thus the number of worms can reduce or explain the variation by about 72%.

Instead of sum of squares, one may consider the mean square as the level of variation. In such a case, the number of worms can reduce the total mean square (or variance) by: (total mean square - residual mean square) / total mean square, or (variance - residual mean square) / variance.

```
> resid.msq <- sum(residuals(lm1)^2)/lm1$df.residual
> Radj <- (var(bloss)- resid.msq)/var(bloss); Radj
[1] 0.69419
```

This is the adjusted R-squared shown in `summary(lm1)` in the above section.

F-test

When the mean square of 'worm' is divided by the mean square of residuals, the result is:

```
> F <- SSW/resid.msq; F
[1] 32.78
```

Using this F value with the two corresponding degrees of freedom (from 'worm' and residuals) the P value for testing the effect of 'worm' can be computed.

```
> pf(F, df1=1, df2=13, lower.tail=FALSE)
[1] 6.9904e-05
```

The function `pf` is used to compute a P value from a given F value together with the two values of the degrees of freedom. The last argument 'lower.tail' is set to FALSE to obtain the right margin of the area under the curve of the F distribution.

In summary, both the regression and analysis of variance give the same conclusion; that number of worms has a significant linear relationship with blood loss. Now the regression line can be drawn.

Regression line, fitted values and residuals

A regression line can be added to the scatter plot with the following command:

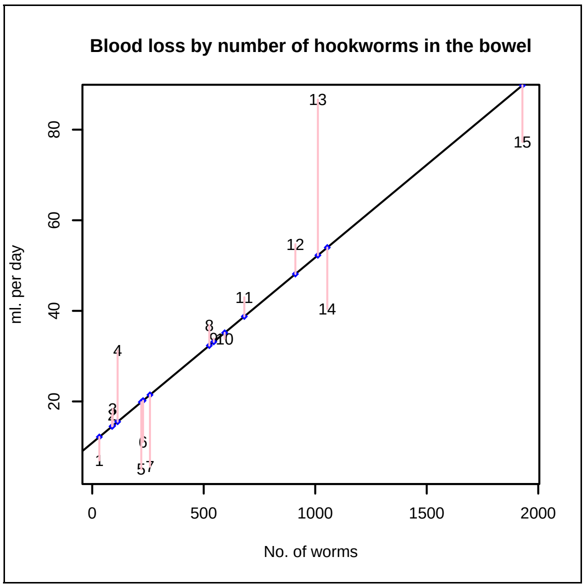
```
> abline(lm1)
```

The regression line has an intercept of 10.8 and a slope of 0.04. The expected value is the value of blood loss estimated from the regression line with a specific value of 'worm'.

```
> points(worm, fitted(lm1), pch=18, col="blue")
```

A residual is the difference between the observed and expected value. The residuals can be drawn by the following command:

```
> segments(worm, bloss, worm, fitted(lm1), col="pink")
```



The actual values of the residuals can be checked from the specific attribute of the defined linear model.

```
> residuals(lm1) -> lm1.res; lm1.res
```

Note that some residuals are positive and some are negative. The 13th residual has the largest value (furthest from the fitted line). The sum of the residuals and the sum of their squares can be checked.

```
> sum(lm1.res); sum(lm1.res ^2)
[1] 3.9968e-15
[1] 2455.5
```

The sum of residuals is close to zero whereas the sum of their squares is the value previously displayed in the summary of the model. The distribution of residuals, if the model fits well, should be normal.

Checking normality of residuals

A common sense approach for checking normality of residuals is to look at the histogram.

```
> hist(lm1.res)
```

The plot from the above command does not suggest that residuals are normally distributed. However, with such a small sample size, it is difficult to draw any conclusion. A better way to check normality is to plot the residuals against the expected normal score or (residual-mean) / standard deviation. A reasonably straight line would indicate normality.

```
> qqnorm(lm1.res)
```

Numerically, Shapiro-Wilk test can also be applied.

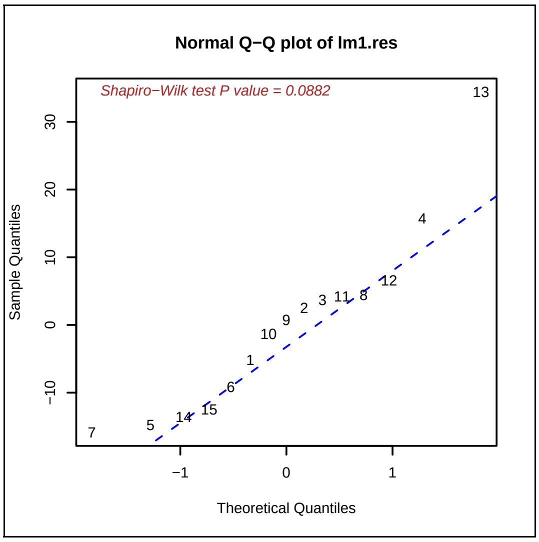
```
> shapiro.test(lm1.res)

        Shapiro-Wilk normality test

data:  residuals (lm1)
W = 0.8978, p-value = 0.0882

> qqline(lm1.res)
```

Epicalc combines the three commands and adds the P value of the test to the graph.

```
> shapiro.qqnorm(lm1.res, type="n")
> qqnorm(lm1.res) -> a
> text(a$x, a$y, labels=as.character(id))
```

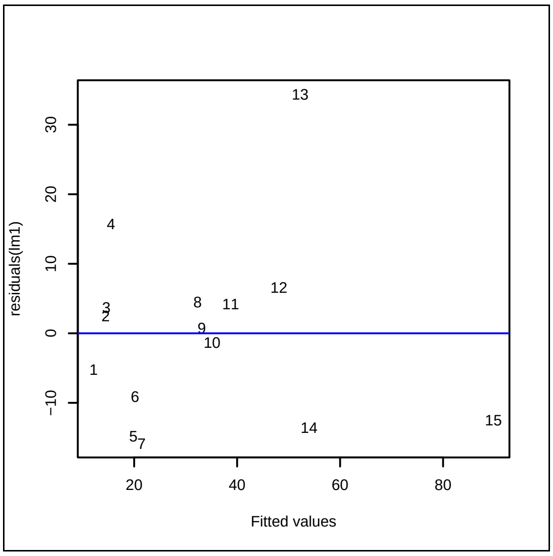
The X and Y coordinates are 'a$x' and 'a$y', respectively.

If the residuals were perfectly normally distributed, the text symbols would have formed along the straight dotted line. The graph suggests that the largest residual (13th) is too high (positive) whereas the smallest value (7th) is not large enough (negative). However, the P value from the Shapiro-Wilk test is 0.08 suggesting that the possibility of residuals being normally distributed cannot be rejected.



Finally, the residuals are plotted against the fitted values to see if there is a pattern.

```
> plot(fitted(lm1), lm1.res, xlab="Fitted values")
> plot(fitted(lm1), lm1.res, xlab="Fitted values", type="n")
> text(fitted(lm1), lm1.res, labels=as.character(id))
> abline(h=0, col="blue")
```



There is no obvious pattern. The residuals are quite independent of the expected values. With this and the above findings from the 'qqnorm' command we may conclude that the residuals are randomly and normally distributed.

The above two diagnostic plots for the model 'lm1' can also be obtained from:

```
> windows(7, 4)
> par(mfrow=c(1,2))
> plot.lm(lm1, which=1:2)
```

Final conclusion

From the analysis, it is clear that blood loss is associated with number of hookworms. On average, each worm may cause 0.04 ml of blood loss. The remaining uncertainty of blood loss, apart from hookworm, is explained by random variation or other factors that were not measured.

Exercise

Load the **SO2** dataset and label the variables using the following commands.

```
> label.var(smoke, "Smoke (mg/cu.m.)")
> label.var(SO2, "SO2 (ppm.)")
```

Using scatter plots and linear regression check whether smoke or SO2 has more influence on logarithm of deaths.

Interpret the results the best simple linear regression.

Chapter 12: Stratified linear regression

Datasets usually contain many variables collected during a study. It is often useful to see the relationship between two variables within the different levels of another third, categorical variable.

Example: Systolic blood pressure

A small survey on blood pressure was carried out. The objective is to see the hypertensive effect of subjects putting additional table salt on their meal.

```
> zap()
> data(BP);  use(BP)
> des()

cross-sectional survey on BP & risk factors
No. of observations =100
  Variable      Class           Description
1 id            integer         id
2 sex           factor          sex
3 sbp           integer         Systolic BP
4 dbp           integer         Diastolic BP
5 saltadd       factor          Salt added on table
6 birthdate     Date

> summ()
cross-sectional survey on BP & risk factors
No. of observations = 100
Var. name  Obs.  mean       median     s.d.   min.       max.
id         100   50.5       50.5       29.01  1          100
sex        100   1.55       2          0.5    1          2
sbp        100   154.34     148        39.3   80         238
dbp        100   98.51      96         22.74  55         158
saltadd     80   1.538      2          0.502  1          2
birthdate  100   1952-10-11 1951-11-17 <NA>   1930-11-14 1975-
  12-08
```

Note that the maximum systolic and diastolic blood pressures are quite high. There are 20 missing values in 'saltadd'. The frequencies of the categorical variables 'sex' and 'saltadd' are now inspected.

```
> summary(data.frame(sex, saltadd))
     sex       saltadd
 male  :45    no  :37
 female:55    yes :43
              NA's:20
```

The next step is to create a new age variable from birthdate. The calculation is based on 12th March 2001, the date of the survey.

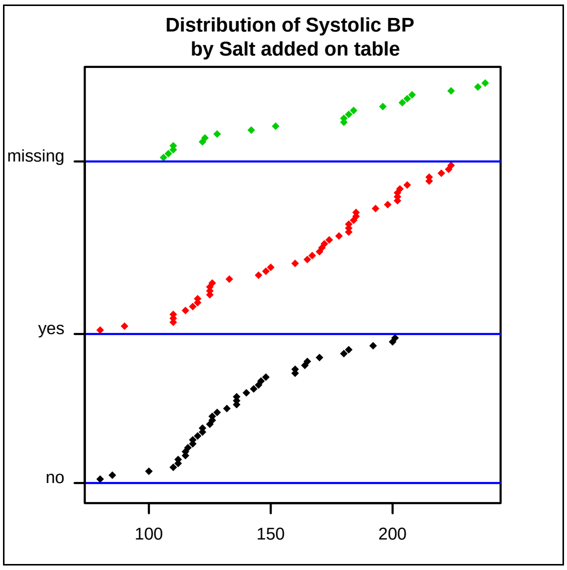
```
> age.in.days <- as.Date("2001-03-12") - birthdate
```

There is a leap year in every four years. Therefore, an average year will have 365.25 days.

```
> class(age.in.days)
[1] "difftime"
> age <- as.numeric(age.in.days)/365.25
```

The function `as.numeric` is needed to transform the units of age (*difftime*); otherwise modelling would not be possible.

```
> summ(sbp, by = saltadd)

For saltadd = no
  Obs.   mean    median   s.d.    min.    max.
  37     137.5   132      29.624  80      201
For saltadd = yes
  Obs.   mean    median   s.d.    min.    max.
  43     163     171      39.39   80      224
For saltadd = missing
  Obs.   mean    median   s.d.    min.    max.
  20     166.9   180      45.428  106     238
```



Recoding missing values into another category

The missing value group has the highest median and average systolic blood pressure. In order to create a new variable with three levels type:

```
> saltadd1 <- saltadd
> levels(saltadd1) <- c("no", "yes", "missing")
> saltadd1[is.na(saltadd)] <- "missing"
> summary(saltadd1)
     no     yes missing
     37      43      20
> summary(aov(age ~ saltadd1))
            Df  Sum Sq Mean Sq F value Pr(>F)
saltadd1     2   114.8    57.4  0.4484   0.64
Residuals   97 12421.8   128.1
```

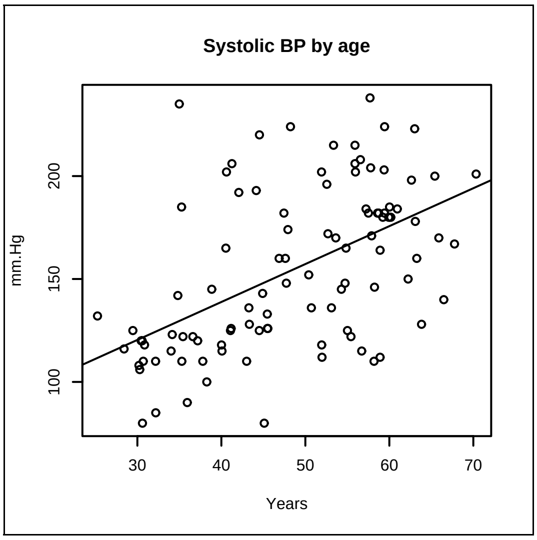
Since there is not enough evidence that the missing group is important and for additional reasons of simplicity, we will ignore this group and continue the analysis with the original 'saltadd' variable consisting of only two levels. Before doing this however, a simple regression model and regression line are first fitted.

```
> lm1 <- lm(sbp ~ age)
> summary(lm1)
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  65.1465    14.8942   4.374 3.05e-05
age           1.8422     0.2997   6.147 1.71e-08
Residual standard error: 33.56 on 98 degrees of freedom
Multiple R-Squared: 0.2782,     Adjusted R-squared: 0.2709
F-statistic: 37.78 on 1 and 98 DF,  p-value: 1.712e-08
```

Although the R-squared is not very high, the P value is small indicating important influence of age on systolic blood pressure.

A scatterplot of age against systolic blood pressure is now shown with the regression line added using the '`abline`' function, previously mentioned in chapter 11. This function can accept many different argument forms, including a regression object. If this object has a 'coef' method, and it returns a vector of length 1, then the value is taken to be the slope of a line through the origin, otherwise the first two values are taken to be the intercept and slope, as is the case for '`lm1`'.

```
> plot(age, sbp, main = "Systolic BP by age", xlab = "Years",
    ylab = "mm.Hg")

> coef(lm1)
(Intercept)         age
    65.1465      1.8422

> abline(lm1)
```



Subsequent exploration of residuals suggests a non-significant deviation from normality and no pattern. Details of this can be adopted from the techniques discussed in the previous chapter and are omitted here. The next step is to provide different plot patterns for different groups of salt habits.

```
> lm2 <- lm(sbp ~ age + saltadd)
> summary(lm2)
====================
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  63.1291    15.7645   4.005 0.000142
age           1.5526     0.3118   4.979 3.81e-06
saltaddyes   22.9094     6.9340   3.304 0.001448
---
Residual standard error: 30.83 on 77 degrees of freedom
Multiple R-Squared: 0.3331,     Adjusted R-squared: 0.3158
F-statistic: 19.23 on 2 and 77 DF,  p-value: 1.68e-07
```

On the average, a one year increment of age increases systolic blood pressure by 1.5 mmHg. Adding table salt increases systolic blood pressure significantly by approximately 23 mmHg.

Similar to the method used in the previous chapter, the following step creates an empty frame for the plots:

```
> plot(age, sbp, main="Systolic BP by age", xlab="Years",
  ylab="mm.Hg", type="n")
```

Add blue hollow circles for subjects who did not add table salt.

```
> points(age[saltadd=="no"], sbp[saltadd=="no"], col="blue")
```

Then add red solid points for those who did add table salt.

```
> points(age[saltadd=="yes"], sbp[saltadd=="yes"], col="red",
  pch = 18)
```

Note that the red dots corresponding to those who added table salt are higher than the blue circles. The final task is to draw two separate regression lines for each group.

Since model 'lm2' contains 3 coefficients, the command abline now requires the argument 'a' as the intercept and 'b' as the slope.

```
> coef(lm2)
(Intercept)         age  saltaddyes
  63.129112    1.552615   22.909449
```

We now have two regression lines to draw, one for each group. The intercept for non-salt users will be the first coefficient and for salt users will be the first plus the third. The slope for both groups is the same. Thus the intercept for the non-salt users is:

```
> a0 <- coef(lm2)[1]
```

For the salt users, the intercept is the first plus the third coefficient:

```
> a1 <- coef(lm2)[1] + coef(lm2)[3]
```

For both groups, the slope is fixed at:

```
> b <- coef(lm2)[2]
```

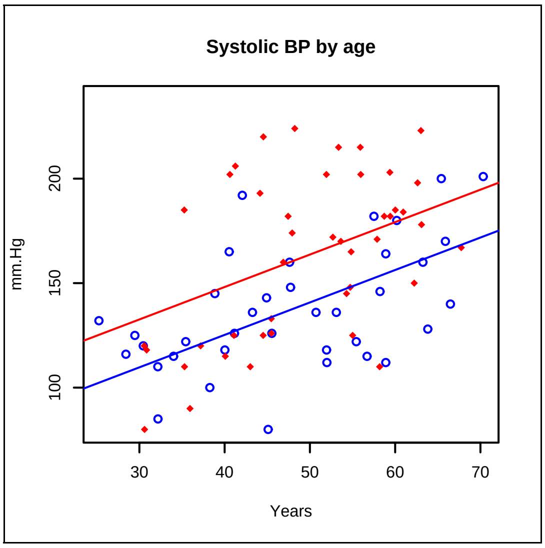
Now the first (lower) regression line is drawn in blue, then the other in red.

```
> abline(a = a0, b, col = "blue")
> abline(a = a1, b, col = "red")
```

Note that X-axis does not start at zero. Thus the intercepts are out of the plot frame.

The red line is for the red points of salt adders and the blue line is for the blue points of non-adders. In this model, age has a constant independent effect on systolic blood pressure.

Look at the distributions of the points of the two colours; the red points are higher than the blue ones but mainly on the right half of the graph. To fit lines with different slopes, a new model with interaction term is created.



The next step is to prepare a model with different slopes (or different 'b' for the abline arguments) for different lines. The model needs an interaction term between 'saltadd' and 'age'.

```
> lm3 <- lm(sbp ~ age * saltadd)
> summary(lm3)
Call:
lm(formula = sbp ~ age * saltadd)
===============
Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)     78.0066    20.3981   3.824 0.000267 ***
age              1.2419     0.4128   3.009 0.003558 **
saltaddyes     -12.2540    31.4574  -0.390 0.697965
age:saltaddyes   0.7199     0.6282   1.146 0.255441
---
Multiple R-Squared: 0.3445,     Adjusted R-squared: 0.3186
F-statistic: 13.31 on 3 and 76 DF,  p-value: 4.528e-07
```

In the formula part of the model, 'age * saltadd' is the same as 'age + saltadd + age:saltadd'. The four coefficients are displayed in the summary of the model. They can also be checked as follows.

```
> coef(lm3)
   (Intercept)          age    saltaddyes  age:saltaddyes
    78.0065572    1.2418547   -12.2539696       0.7198851
```

The first coefficient is the intercept of the fitted line among non-salt users.

For the intercept of the salt users, the second term and the fourth are all zero (since age is zero) but the third should be kept as such. This term is negative. The intercept of salt users is therefore lower than that of the non-users.

```
> a0 <- coef(lm3)[1]
> a1 <- coef(lm3)[1] + coef(lm3)[3]
```

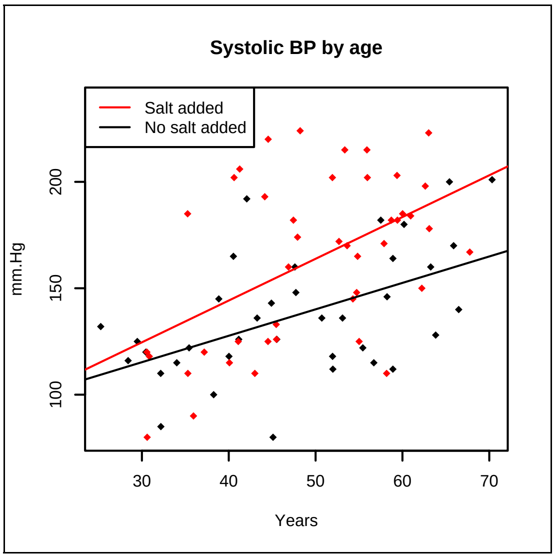
For the slope of the non-salt users, the second coefficient alone is enough since the first and the third are not involved with each unit of increment of age and the fourth term has 'saltadd' being 0. The slope for the salt users group includes the second and the fourth coefficients since 'saltaddyes' is 1.

```
> b0 <- coef(lm3)[2]
> b1 <- coef(lm3)[2] + coef(lm3)[4]
```

These terms are used to draw the two regression lines.

Redraw the graph but this time with black representing the non-salt adders.

```
> plot(age, sbp, main="Systolic BP by age", xlab="Years",
  ylab="mm.Hg", pch=18, col=as.numeric(saltadd))
> abline(a = a0, b = b0, col = 1)
> abline(a = a1, b = b1, col = 2)
> legend("topleft", legend = c("Salt added", "No salt added"),
  lty=1, col=c("red","black"))
```



Note that '`as.numeric(saltadd)`' converts the factor levels into the integers 1 (black) and 2 (red), representing the non-salt adders and the salt adders, respectively. These colour codes come from the **R** colour *palette*.

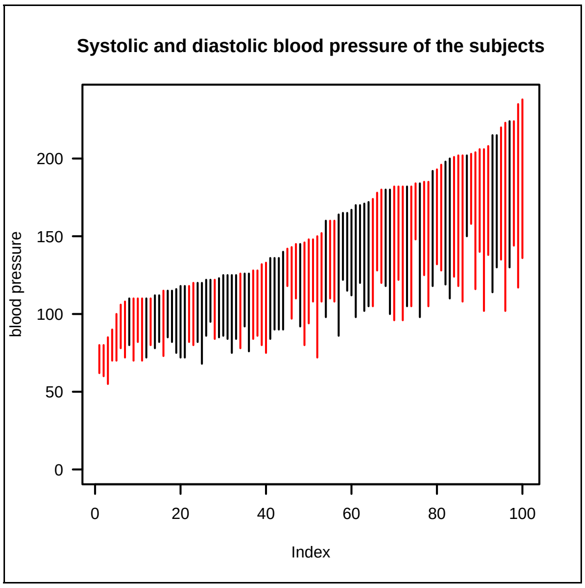
This model suggests that at the young age, the systolic blood pressure of two groups are not much different as the two lines are close together on the left of the plot. For example, at the age of 25, the difference is 5.7mmHg. Increasing age increases the difference between the two groups. At 70 years of age, the difference is as great as 38mmHg. (For simplicity, the procedures for computation of these two levels of difference are skipped in these notes). In this aspect, age modifies the effect of adding table salt.

On the other hand the slope of age is 1.24mmHg per year among those who did not add salt but becomes 1.24+0.72 = 1.96mmHg among the salt adders. Thus, salt adding modifies the effect of age. Interaction is a statistical term whereas effect modification is the equivalent epidemiological term.

The coefficient of the interaction term 'age:saltaddyes' is not statistically significant. The two slopes just differ by chance.

Exercise

Plot systolic and diastolic blood pressures of the subjects, use red colour of males and blue for females as shown in the following figure. [Hint: `segments`]



Check whether there is any significant difference of diastolic blood pressure among males and females after adjustment for age.

Chapter 13: Curvilinear Relationship

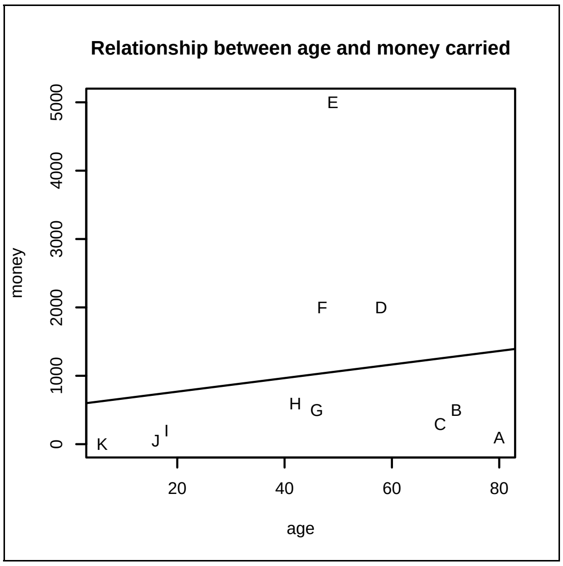
Example: Money carrying and age

This chapter returns to the family data and explores the relationship between money carried and age.

```
> zap()
> data(Familydata)
> use(Familydata)
> des()
> plot(age, money, pch=" ")
```

The above command is equivalent to:

```
> plot(age, money, type="n")
```



To put the 'code' as text at the points, add a title and a regression line, type the following:

```
> text(age, money, labels = code)
> title("Relationship between age and money carried")
> lm1 <- lm(money ~ age)
> abline(lm1)
```

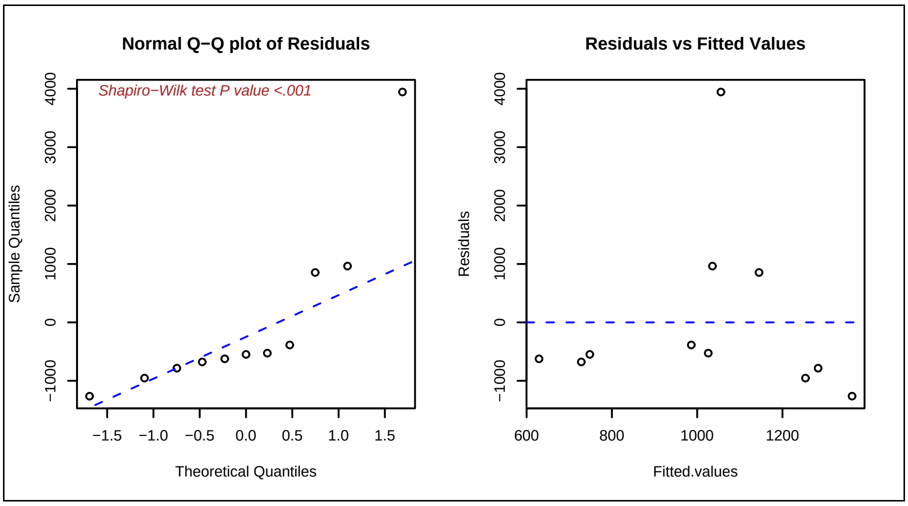
The '`lm1`' object can be inspected by using the `summary` function.

```
> summary(lm1)
============
Residual standard error: 1560 on 9 degrees of freedom
Multiple R-Squared: 0.0254,    Adjusted R-squared: -0.08285
F-statistic: 0.2349 on 1 and 9 DF,  p-value: 0.6395
```

The R-squared is very small indicating a poor fit. This is confirmed by the poor fit of the regression line in the previous graph. People around 40-60 years old tend to carry more money than those in other age groups.

Checking residuals reveals the following results.

```
> Residuals <- resid(lm1)
> Fitted.values <- fitted(lm1)
> windows(9,5)
> opar <- par(mfrow=c(1,2))
> shapiro.qqnorm(Residuals)
> plot(Fitted.values, Residuals, main="Residuals vs Fitted")
> abline(h=0, lty=3, col="blue")
```



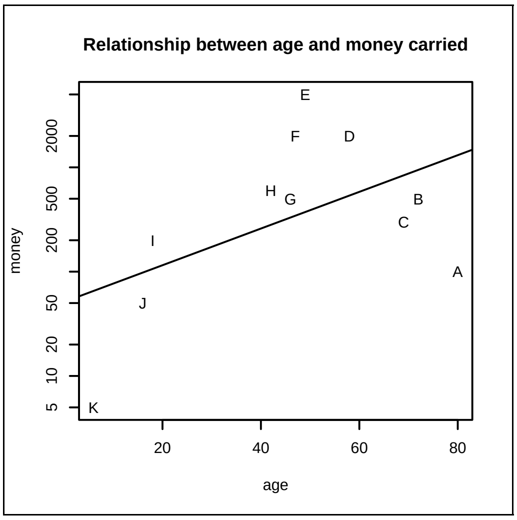
From the above plots the residuals are not normally distributed.

To reset the graphics device back to the orignal settings type:

```
> par(opar)
```

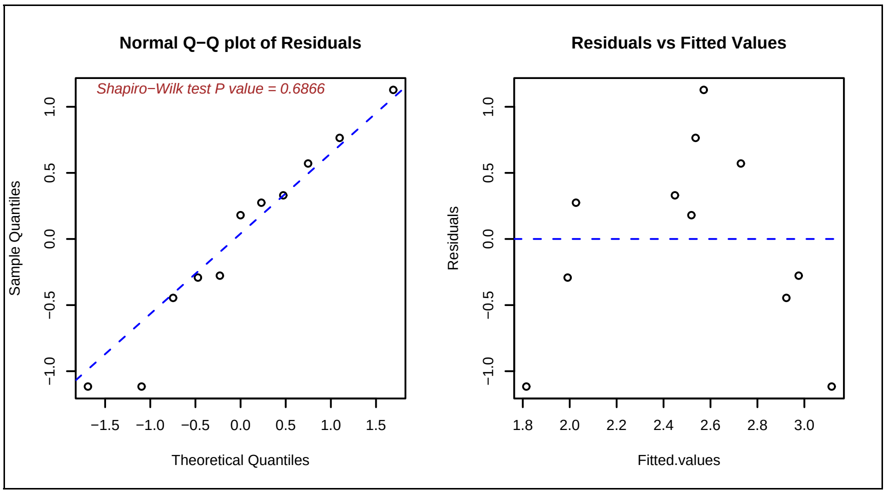
Variation in money usually has an exponential distribution. Taking logarithms may help improve the model fit.

```
> plot(age, money, type="n", log = "y",
  main = "Relationship between age and money carried")
> text(age, money, labels = code)
> lm2 <- lm(log10(money) ~ age)
> abline(lm2)
```



With the log scale of the y-axis, the distribution of the relationship tends to be curvilinear. Drawing a straight regression line through these points is thus not appropriate. Residuals can be checked as follows:

```
> Residuals <- resid(lm2)
> Fitted.values <- fitted(lm2)
> windows(9,5)
> opar <- par(mfrow=c(1,2))
> shapiro.qqnorm(Residuals)
> plot(Fitted.values, Residuals, main="Residuals vs Fitted")
> abline(h=0, lty=3, col="blue")
```



The residuals now look normally distributed. However, the values of the high residuals are in the middle of the range of the fitted values, indicating that perhaps we need to include a quadratic term of age in the model.

To fit a regression line under the log scale but with a linear (non-log scale) value would be too complicated. A better way would be to transform 'money' into a new variable on a log base 10 scale and fit a new model with a quadratic term of age.

```
> lm3 <- lm(log10(money) ~ age + I(age^2))
> summary(lm3)
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.102650   0.338502    0.30  0.76944
age          0.125355   0.017641    7.11  0.00010
I(age^2)    -0.001268   0.000201   -6.30  0.00023

Residual standard error: 0.332 on 8 degrees of freedom
Multiple R-Squared: 0.875,      Adjusted R-squared: 0.844
F-statistic:   28 on 2 and 8 DF,  p-value: 0.000243
```

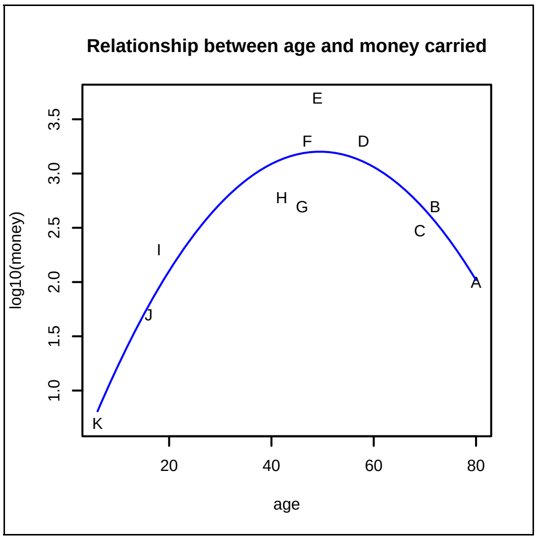
Both the adjusted and non-adjusted R-squared values are high. Adding the quadratic age term improves the model substantially and is statistically significant. The next step is to fit a regression line, a task that is not straightforward.

A regression line is a line joining fitted values. There are too few points of fitted values in the model. A new data frame is now created to include a new 'age' variable ranging from 6 to 80 (which is the age range of our subjects) and the corresponding age-squared term.

```
> new <- data.frame(age = 6:80, age2 = (6:80)^2)
```

Then the predicted values of this data frame are computed based on the last model.

```
> predict1 <- predict.lm(lm3, new)
> plot(age, log10(money), type="n", ylab = "log10(money)",
   main="Relationship between age and money carried",)
> text(age, log10(money), labels = code)
> lines(new$age, predict1, col = "blue")
```



Maximum value in the quadratic model

The quadratic model explains that, a young person such as "K" who is 5 years old carries very little money. The money carried increases with age and peaks between 40-50 years of age. Then the value drops when age increases.

The maximum predicted value is

```
> max(predict1)
[1] 3.2012
```

The corresponding money value is

```
> 10^max(predict1)
[1] 1589.4
```

The corresponding age is

```
> new$age[which.max(predict1)]
[1] 49
```

However, more precise mathematical calculation from the coefficients can be obtained as follows:

```
> coef(lm4)
(Intercept)         age    I(age^2)
  0.1026501   0.1253546  -0.0012677

> a <- coef(lm3)[3]
> b <- coef(lm3)[2]
> c <- coef(lm3)[1]
> x <- -b/(2*a); x   # 49.441
```

The corresponding value in the Y-axis is

```
> y <- a * x^2 + b * x + c
> y   # 3.20148
```

Finally, the corresponding money is therefore:

```
> 10^y  # 1590.3
```

The conclusion from the model is that at the age of 49 years, an average person will carry approximately 1,590 baht. This amount is lower than the actual value of money carried by "E", which is 5,000 baht or more than three times higher.

```
> 10^(log10(money)[code=="E"]-y)  # 3.1441
```

Stratified curvilinear model

There are both males and females in the family. As an exercise, two parallel curves will be used to fit the data.

```
> lm4 <- lm(log10(money) ~ sex + age + I(age^2))
> summary(lm4)
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.027252   0.338084    0.08  0.93801
sexM         0.239320   0.207432    1.15  0.28648
age          0.126284   0.017305    7.30  0.00016
I(age^2)    -0.001288   0.000198   -6.51  0.00033

Residual standard error: 0.325 on 7 degrees of freedom
Multiple R-Squared: 0.895,      Adjusted R-squared: 0.85
F-statistic: 19.9 on 3 and 7 DF,  p-value: 0.000834
```

The model '`lm4`' gives a slightly higher R-squared than that from '`lm3`'. Sex ("M" compared with "F") is not significant. We use this model for a plotting exercise.

```
> plot(age, log10(money), type="n", ylab = "log10(money)"
    main = "Relationship between age and money carried")
> text(age, log10(money), labels=code, col=unclass(sex))
```

Note that the first line is the same as previous plots. The second line however, differentiates sex with colour. When 'sex', which is a factor, is unclassed, the values become the numerical order of the levels. "F" is coded 1 and "M" is coded 2. as given in the default colour palette of **R**.

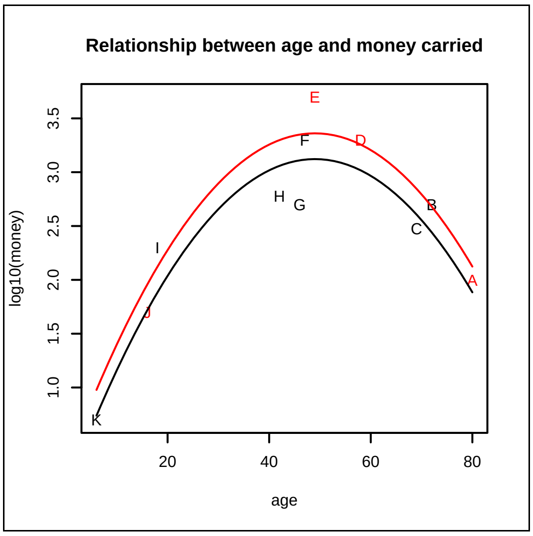
```
> age.frame2.male <- data.frame(age = 6:80, age2 = (6:80)^2,
   sex = factor ("M"))
> predict2.male <- predict.lm(lm4, age.frame2.male)
```

The first command creates a data frame containing variables used in '`lm4`'. Note that the 'sex' here is confined to males. The second command creates a new vector based on '`lm4`' and the new data frame. First we draw the line for males.

```
> lines(age.frame2.male$age, predict2.male, col = 2)
```

Finally the line for females.

```
> age.frame2.female <- data.frame(age = 6:80, age2 = (6:80)^2,
  sex = factor("F"))
> predict2.female <- predict.lm(lm4, age.frame2.female)
> lines(age.frame2.female$age, predict2.female, col=1)
```



The red line is located consistently above the black line, since our model did not include an interaction term. For every value of age, males tend to carry 102.4 or 1.738 times more money than females. The difference is however, not significant.

From age to age group

So far, we have analysed the effect of age as a continuous variable. In most of the epidemiological data analysis, age is often transformed to a categorical variable by cutting it into age groups. For this small dataset, we divide the subjects into children, adults and elderly subjects with cut points of 20 and 40 years with the two extremes of 0 and 85 years.

```
> agegr <- cut(age, breaks = c(0, 20, 60, 85),
   labels = c("Child", "Adult", "Elder"))
```

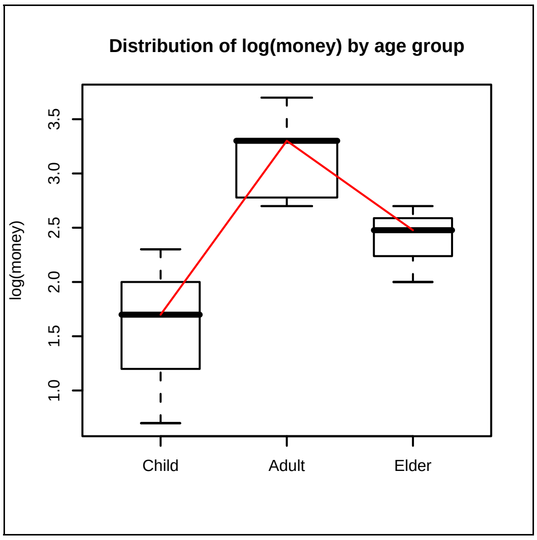
This method of cutting has already been explained in Chapter 2. Here, we put the specific labels to replace the default bin names of "(0,20]","(20,60]" and "(60,80]".

To illustrate the change of log(money) by age, a series of box plots are drawn with the statistical parameters stored in a new object 'a'.

```
> a <- boxplot(logmoney ~ agegr, varwidth = TRUE)
```

Then lines are drawn to join the median of log(money) of the age groups, which are in the third row of 'a'.

```
> lines(x = 1:3, y = a$stats[3, ], col = "red")
> title(main = "Distribution of log(money) by age group",
   ylab = "log(money)")
```



Modelling with a categorical independent variable

A new model is now fit adding the categorical variable 'agegr'.

```
> lm5 <- lm(log10(money) ~ sex + agegr)
> summary(lm5)
=================== Lines omitted ===============
            Estimate Std. Error t value Pr(>|t|)
(Intercept)    1.510      0.343    4.40   0.0031
sexM           0.169      0.351    0.48   0.6436
agegrAdult     1.578      0.408    3.87   0.0062
agegrElder     0.826      0.456    1.81   0.1129
=================== Lines omitted ===============
```

There are two age group parameters in the model; "Adult" and "Elder". The first level, "Child", is omitted since it is the referent level. This means the other levels will be compared to this level. Adults carried $10^{1.578}$ or approximately 38 times more money than children, which is statistically significant. Elders carried $10^{0.8257}$ = 6.7 times more money than children, but is not statistically significant.

We could check the pattern of contrasts as follows:

```
> contrasts(agegr)
       Adult Elder
Child      0     0
Adult      1     0
Elder      0     1
```

The columns of the matrix are the variables appearing in the model. The rows show all the levels. The column 'Adult' in the model is equal to 1 when agegr is equal to "Adult" and zero otherwise. The column 'Elder' is 1 when 'agegr' is "Elder" and zero otherwise. There is no column of 'Child'. When both 'Adult' and 'Elder' are equal to zero, the model then predicts the value of 'agegr' being "Child". If "Adult" is required to be the referent level, the contrasts can be changed.

```
> contrasts(agegr) <- contr.treatment(levels(agegr), base=2)
```

The above command changes the referent group to level 2.

```
> contrasts(agegr)
       Child Elder
Child      1     0
Adult      0     0
Elder      0     1
```

The 'Adult' column is now missing. Other tpes of contrast can also be specified. See the references for more details.

```
> summary(lm(log10(money) ~ sex + agegr))
================== Lines omitted =================
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)     3.088      0.286   10.78  1.3e-05
sexM            0.169      0.351    0.48   0.6436
agegrChild     -1.578      0.408   -3.87   0.0062
agegrElder     -0.752      0.408   -1.84   0.1079
================== Lines omitted =================
```

Note that he coefficient of 'Child' is the negative of that of 'Adult' from model '`lm5`'. Moreover, elderly persons did not carry significantly less money than adults.

References

Venables, W. N. and Ripley, B. D. (2002) Modern Applied Statistics with S. Fourth edition. Springer.

Exercise

What will happen in '`lm3`' if log base 2 is used instead of log base 10? Would the conclusion be the same?

Chapter 14: Generalized Linear Models

From lm to glm

Linear modelling using the `lm` function is based on the least squares method. The concept is to minimise the sum of squares of residuals. Modelling from `lm` is equivalent to that of analysis of variance using the `aov` function. The only difference is that the former focuses on coefficients of the independent variables whereas the latter focuses on their sums of squares.

Generalized linear modelling (GLM) is, as it is called, more general that just linear modelling. The method is based on the likelihood function. When the likelihood is maximised, the coefficients and variances (and subsequently standard errors) of independent variables are achieved. While classical linear modelling assumes the outcome variable is defined on a continuous scale, such as blood loss in the previous examples, (as well as assuming normality of errors and constant variance), GLM can handle outcomes that are expressed as proportions, Poisson distributed (counts) and others such as those from the gamma and negative binomial distributions.

We will first start with the outcome on a continuous scale as in the previous example of blood loss and hookworm infection.

```
> zap()
> data(Suwit)
> use(Suwit)
> bloodloss.lm <- lm(bloss ~ worm)
> summary(bloodloss.lm)
```

The results are already shown in the previous chapter.

Now we perform a generalised linear regression model using the function `glm`. For the `glm` function the default *family* is the Gaussian distribution, and so the 'family' argument can be omitted.

```
> bloodloss.glm <- glm(bloss ~ worm)
> summary(bloodloss.glm)
Call:
glm(formula = bloss ~ worm)

Deviance Residuals:
     Min        1Q    Median        3Q       Max
-15.8461  -10.8118    0.7502    4.3562   34.3896

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) 10.847327   5.308569   2.043   0.0618
worm         0.040922   0.007147   5.725 6.99e-05

(Dispersion parameter for gaussian family taken to be 188.882)

    Null deviance: 8647.0  on 14  degrees of freedom
Residual deviance: 2455.5  on 13  degrees of freedom
AIC: 125.04

Number of Fisher Scoring iterations: 2
```

Using the same data frame and the same formula, i.e. 'bloss ~ worm', the results from 'lm' and 'glm' for residuals (called deviance residuals in 'glm'), coefficients and standard errors are the same. However, there are more attributes of the latter than the former.

Model attributes

```
> attributes(bloodloss.lm)
$names
 [1] "coefficients"  "residuals"   "effects"     "rank"
 [5] "fitted.values" "assign"      "qr"          "df.residual"
 [9] "xlevels"       "call"        "terms"       "model"
$class
[1] "lm"

> attributes(bloodloss.glm)
$names
 [1] "coefficients" "residuals"  "fitted.values"
 [4] "effects"      "R"          "rank"
 [7] "qr"           "family"     "linear.predictors"
[10] "deviance"     "aic"        "null.deviance"
[13] "iter"         "weights"    "prior.weights"
[16] "df.residual"  "df.null"    "y"
[19] "converged"    "boundary"   "model"
[22] "call"         "formula"    "terms"
[25] "data"         "offset"     "control"
[28] "method"       "contrasts"  "xlevels"
$class
[1] "glm" "lm"
```

Note that 'bloodloss.glm' also has class as *lm* in addition to its own *glm*. The two sets of attributes are similar with more sub-elements for the 'bloodloss.glm '. Sub-elements of the same names are essentially the same. In this setting, the 'deviance' from the glm command is equal to the sum of squares of the residuals.

```
> sum(bloodloss.glm$residuals^2)
[1] 2455.468
> bloodloss.glm$deviance
[1] 2455.468
```

Similarly, the 'null.deviance' is equal to the total sum of squares of the difference of individual amount of blood loss from the mean blood loss.

```
> sum((bloss-mean(bloss))^2)
[1] 8647.044
> bloodloss.glm$null.deviance
[1] 8647.044
```

Some of the attributes in of the 'glm' are rarely used but some, such as 'aic', are very helpful. There will be further discussion on this in future chapters.

Attributes of model summary

```
> attributes(summary(bloodloss.lm))
$names
 [1] "call"     "terms"  "residuals"  "coefficients"
 [5] "aliased"  "sigma"  "df"         "r.squared"
 [9] "adj.r.squared"  "fstatistic"    "cov.unscaled"
$class
[1] "summary.lm"

> attributes(summary(bloodloss.glm))
$names
$names
 [1] "call"           "terms"          "family"
 [4] "deviance"       "aic"            "contrasts"
 [7] "df.residual"    "null.deviance"  "df.null"
[10] "iter"           "deviance.resid" "coefficients"
[13] "aliased"        "dispersion"     "df"
[16] "cov.unscaled"   "cov.scaled"

$class
[1] "summary.glm"
```

A large proportion of the elements of both sets of attributes repeat those of the models. The additional attributes include the R squared in the 'lm' model and the covariance matrix ('cov.unscaled') in both models. This covariance matrix is used for calculation of the standard errors and 95% confidence intervals of the coefficients.

Covariance matrix

When there are two or more explanatory variables, and they are not independent, the collective variation is denoted as covariance (compared to variance for a single variable). It is stored as a symmetrical matrix since one variable can covary with each of the others. A covariance matrix can be 'scaled' or 'unscaled'. The one from the 'lm' model gives 'cov.unscaled' while 'glm' gives both.

```
> vcov(bloodloss.glm)   # or summary(bloodloss.glm)$cov.scaled
            (Intercept)          worm
(Intercept) 28.18090491 -2.822006e-02
worm        -0.02822006  5.108629e-05
> summary(bloodloss.glm)$cov.unscaled
              (Intercept)          worm
(Intercept)  0.1491983716 -1.494057e-04
worm        -0.0001494057  2.704665e-07
```

The latter covariance matrix can also be obtained from the summary of the ordinary linear model.

```
> summary(bloodloss.lm)$cov.unscaled
```

The scaling factor is, in fact, the dispersion, or sigma squared, which is the sum of squares of residuals divided by degrees of freedom of the residual. Thus the first matrix can be obtained from

```
> summary(bloodloss.glm)$cov.unscaled *
  summary(bloodloss.glm)$dispersion
```

or

```
> summary(bloodloss.lm)$cov.unscaled *
  summary(bloodloss.lm)$sigma^2
```

or

```
> summary(bloodloss.lm)$cov.unscaled *
  sum(summary(bloodloss.lm)$residuals^2)/13
```

The scaled covariance matrix is used for computing standard errors of the coefficients. The diagonal term of this matrix where the row name is the same as the column name is the value of variance of the coefficient under the same name. Taking the square root of this term will result in the standard error of the coefficient.

Computation of standard errors, t values and 95% confidence intervals

The standard error of 'worm' is

```
> vcov(bloodloss.glm)[2,2]^.5 -> se2
> se2
[1] 0.0071475
```

This can be checked against the summary of the coefficients.

```
> coef(summary(bloodloss.glm))
             Estimate Std. Error  t value    Pr(>|t|)
(Intercept) 10.847327 5.3085690  2.043362  0.06183205
worm         0.040922 0.0071475  5.725392  0.00006990
```

Subsequently, the 't value' can be computed from division of the coefficient by the standard error:

```
> coef(summary(bloodloss.glm))[2,1] /
  summary(bloodloss.glm)$cov.scaled[2,2]^.5 -> t2
> t2
```

or

```
> 0.04092205 / 0.007147467 # 5.7254
```

The P value is the probability that 't' can be at this or a more extreme value. The more extreme can be on both sides or signs of the t value. Therefore, the P value is computed from

```
> pt(q=t2, df=13, lower.tail=FALSE) * 2
[1] 6.9904e-05
```

This value is equal to that in the summary of the coefficients. More details on the computation of a probability from the t distribution can be search from 'help(TDist)' or 'help(pt)'.

Finally to compute the 95% confidence interval:

```
> beta2 <- coef(summary(bloodloss.glm))[2,1]; beta2
[1] 0.04092205
> ci2 <- beta2 + qt(c(0.025, 0.975), 13)*se2; ci2
[1] 0.02548089 0.05636321
```

In fact, **R** has a command to compute the 95% confidence interval of the model as follows:

```
> confint(bloodloss.lm)
                 2.5 %    97.5 %
(Intercept) -0.621139 22.315793
worm         0.025481  0.056363
```

The results are the same but faster. Note that the command `confint(bloodloss.glm)` gives a slightly different confidence interval. This is because the function uses the normal distribution instead of t distribution and therefore it is not as appropriate.

Other parts of 'glm'

As mentioned before, the linear modelling or 'lm', after being generalized to become 'glm', can accommodate more choices of outcome variables. The model is said to have a *family*. To check the family:

```
> family(bloodloss.glm) # or bloodloss$family
Family: gaussian
Link function: identity
```

Modelling by `lm` is equivalent to `glm` with family being 'gaussian'. The link function is 'identity', which means that the outcome variable is not transformed. Other types of 'family' and 'link' will be demonstrated in subsequent chapters.

Since the link function is 'identity', the 15 values of the linear predictors for this family of 'glm' are the same as the fitted values (of both the 'lm' and 'glm' models).

```
> all(fitted(bloodloss.glm) == predict(bloodloss.glm))
 [1] TRUE
```

The 'glm' summarises the error using the 'deviance'. For the linear model, this value is equal to the sum of squares of the residuals.

```
> bloodloss.glm$deviance
[1] 2455.468

> sum(summary(bloodloss.lm)$res^2)
[1] 2455.468
```

The interpretation of the error is the same as from the linear model; a larger deviance indicates a poorer fit.

Generalized linear modelling employs numerical iterations to achieve maximum likelihood. The value of the maximum likelihood is small because it is the product of probabilities. Its logarithmic form is therefore better to handle. The maximum log likelihood can be obtained from the following function:

```
> logLik(bloodloss.glm)
'log Lik.' -59.51925 (df=3).
```

The higher (less negative) the log likelihood is, the better the model fits. However, each model has its own explanatory parameters. Having too many parameters can be inefficient. When fitting models one always strives for parsimony. An attribute of a model that balances the log-likelihood and the number of parameters is the AIC value. It is abbreviated from "Akaike Information Criterion" and is equal to -2×log-likelihood + k×*npar*, where *k* is the penalty factor (usually 2) and *npar* represents the number of parameters in the fitted model. A high likelihood or good fit will result in a low AIC value. However, a large number of parameters also results in a high AIC. The number of parameters of this model is 3. The AIC is therefore:

```
> -2*as.numeric(logLik(bloodloss.glm))+2*3
[1] 125.0385

> AIC(bloodloss.glm)
[1] 125.0385
```

The AIC is very useful when choosing between models from the same dataset. This and other important attributes will be discussed in more details in subsequent chapters.

References

Dobson, A. J. (1990). An Introduction to Generalized Linear Models. London: Chapman and Hall.

McCullagh P. and Nelder, J. A. (1989). Generalized Linear Models. London: Chapman and Hall.

Exercise

In the dataset **BP**, use the `glm` command to analyse models predicting systolic blood pressure from age and adding table salt with and without the interaction term. Use the AIC to choose the most efficient model. Check the assumptions of normality.

Chapter 15: Logistic Regression

Distribution of binary outcome

In epidemiological data, most of the outcomes are often binary or dichotomous. For example, in the investigation of the cause of a disease, the status of the outcome, the disease, is diseased vs non-diseased. For a mortality study, the outcome is usually died vs survived.

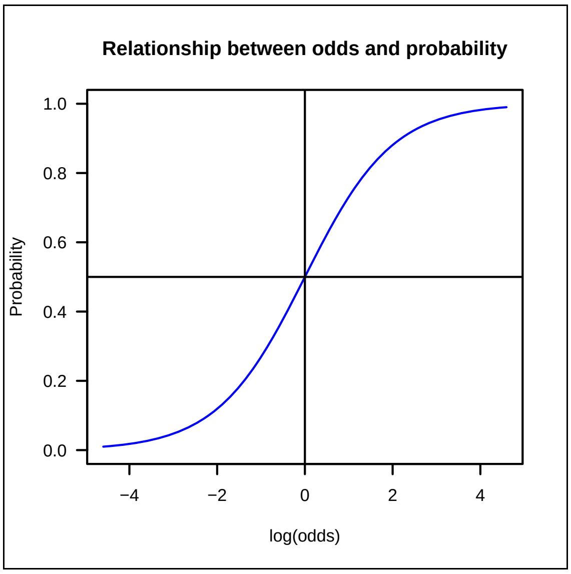
For a continuous variable such as weight or height, the single representative number for the population or sample is the mean or median. For dichotomous data, the representative number is the proportion or percentage of one type of the outcome. For example, 'prevalence' is the proportion of the population with the disease of interest. Case-fatality is the proportion of deaths among the people with the disease.

The other related term is 'probability'. Proportion is a simple straightforward term. Probability denotes the likeliness, which is more theoretical. In the case of a dichotomous variable, the proportion is used as the estimated probability.

For computation, having the outcome is often represented with 1 and 0 otherwise. The prevalence is then the mean of diseased values among the study sample. For example, if there are 50 subjects, 7 with disease (coded 1), 43 without disease (coded 0), then the mean is 7/50 = 0.14, which is the prevalence.

Probability is useful due its simplicity. For complex calculations such as logistic regression, log(odds) or logit is more feasible. If P is the probability of having a disease, 1-P is probability of not having the disease. The odds is thus P/(1-P). The relationship between probability and odds, mainly log(odds) can be plotted as follows.

```
> p <- seq(from=0, to=1, by=.01)
> odds <- p/(1-p)
> plot(log(odds), p, type="l", col="blue", ylab="Probability",
  main="Relationship between odds and probability", las=1)
> abline(h=.5)
> abline(v=0)
```



The probability has a minimum of 0, maximum of 1 and mid value of 0.5. The odds has its corresponding values at 0, infinity and 1. Log(odds), or often called 'logit', has a linear increment with corresponding extremes of -infinity and +infinity and 0 for the mid-point. The curve is called a logistic curve. Being on a linear and well-balanced scale, the logit is a more appropriate scale for a binary outcome than the probability itself. Modelling logit(Y|**X**) ~ **βX** is the general form of logistic regression. It means that the logit of Y given **X** (or under the condition of **X**), where **X** denotes one or more independent variables, can be determined by the sum of products between each specific coefficient with its value of X.

Suppose there are independent or exposure variables: X_1 and X_2. **βX** would be $\beta_0 + \beta_1 X_1 + \beta_2 X_2$, where β_0 is the intercept.

In the medical field, the binary (also called dichotomous) outcome Y is often disease vs non-disease, dead vs alive, etc. The **X** can be age, sex, and other prognostic variables. Among these X variables, one or a few are under testing of the specific hypothesis. Others are potential confounders, sometimes called co-variates.

Mathematically, it turns out that $Pr(Y|\mathbf{X})$ is equal to $exp(\beta\mathbf{X})/(1 + exp(\beta\mathbf{X}))$. Hence, logistic regression is often used to compute the probability of an outcome under a given set of exposures. For example, prediction of probability of getting a disease under a given set of age, sex, and behaviour groups, etc.

Example: Tooth decay

The dataset **Decay** is a simple dataset containing two variables: 'decay', which is binary and 'strep', which is a continuous variable.

```
> zap()
> data(Decay)
> use(Decay)
> des()
No. of observations =436
  Variable      Class          Description
1 decay         numeric        Any decayed tooth
2 strep         numeric        CFU of mutan strep.

> summ()
No. of observations =436
  Var. name Obs.  mean   median  s.d.   min.   max.
1 decay     436   0.63   1       0.48   0      1
2 strep     436   95.25  105     53.5   0.5    152.5
```

The outcome variable is 'decay', which indicates whether a person has at least one decayed tooth (1) or not (0). The exposure variable is 'strep', the number of colony forming units (CFU) of streptococci, a group of bacteria suspected to cause tooth decay.

The prevalence of having decayed teeth is equal to the mean of the 'decay' variable, i.e. 0.63. To look at the 'strep' variable type:

```
> summ(strep)
```

The plot shows that the vast majority have the value at about 150. Since the natural distribution of bacteria is logarithmic, a transformed variable is created and used as the independent variable.

```
> log10.strep <- log10(strep)
> label.var(log10.strep, "Log strep base 10")
> glm0 <- glm(decay~log10.strep, family=binomial, data=.data)
> summary(glm0)
===============
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.554      0.518   -4.93  8.4e-07
log10.strep    1.681      0.276    6.08  1.2e-09
===============
AIC: 535.83
```

Both the coefficients of the intercept and 'log10.strep' are statistically significant.

`Pr(>|z|)` for 'log10.strep' is the P value from Wald's test. This tests whether the co-efficient, 1.681, is significantly different from 0. In this case it is.

The estimated intercept is -2.554. This means that when log10.strep is 0 (or strep equals 1 CFU), the logit of having at least a decayed tooth is -2.55. We can then calculate the baseline odds and probability.

```
> exp(-2.554) -> baseline.odds
> baseline.odds
[1] 0.07777
> baseline.odds/(1+baseline.odds) -> baseline.prob
> baseline.prob
[1] 0.072158
```

There is an odds of 0.077 or a probability of 7.2% of having at least one decayed tooth if the number of CFU of the mutan strep is at 1 CFU.

The coefficient of log10.strep is 1.681. For every unit increment of log10(strep), or an increment of 10 CFU, the logit will increase by 1.681. This increment of logit is constant but not the increment of probability because the latter is not on a linear scale. The probability at each point of CFU is computed by replacing both coefficients obtained from the model. For example, at 100 CFU, the probability is:

```
> coef(glm0)[1] + log10(100)*coef(glm0)[2]
(Intercept)
     0.8078
```

To see the relationship for the whole dataset:

```
> plot(log10.strep, fitted(glm0))
```

A logistic nature of the curve is partly demonstrated. To make it clearer, the ranges of X and Y axes are both expanded to allow a more extensive curve fitting.

```
> plot(log10.strep, fitted(glm0), xlim = c(-2,4),
  ylim=c(0,1), xlab=" ", ylab=" ", xaxt="n", las=1)
```

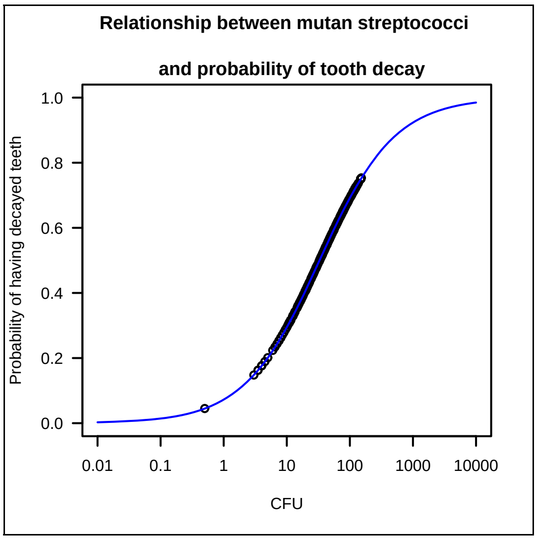
Another vector of the same name 'log10.strep' is created in the form of a data frame for plotting a fitted line on the same graph.

```
> newdata <- data.frame(log10.strep=seq(from=-2, to=4, by=.01))
> predicted.line <- predict.glm(glm0,newdata,type="response")
```

The values for predicted line on the above command must be on the same scale as the 'response' variable. Since the response is either 0 or 1, the predicted line would be in between, ie. the predicted probability for each value of log10(strep).

```
> lines(newdata$log10.strep, predicted.line, col="blue")

> axis(side=1, at=-2:4, labels=as.character(10^(-2:4)))

> title(main="Relationship between mutan streptococci \n
  and probability of tooth decay", xlab="CFU",
  ylab="Probability of having decayed teeth")
```

Note the use of the '\n' in the command above to separate a long title into two lines.



Logistic regression with a binary independent variable

The above example of caries data has a continuous variable 'log10.strep' as the key independent variable. In most epidemiological datasets, the independent variables are often categorical. Remember that we have a dataset on outbreak of food poisoning in Thailand analysed in Chapters 7-9. In this chapter, we will use logistic regression to fit a model when the suspected causes are categorical variables. Readers are advised to compare the results of logistic regression in this chapter with those from the stratified analysis in previous chapters.

```
> zap()
> load("chapter9.Rdata")
> use(.data)
> des()
```

We model 'case' as the binary outcome variable and take 'eclair.eat' as the only explanatory variable.

```
> glm0 <- glm(case ~ eclair.eat, family=binomial, data=.data)
> summary(glm0)
Coefficients:
               Estimate Std. Error z value Pr(>|z|)
(Intercept)      -2.923      0.265  -11.03   <2e-16
eclair.eatTRUE    3.167      0.276   11.48   <2e-16
=================== Lines omitted =================
```

The above part of the display is actually a matrix obtained from:

```
> coef(summary(glm0))
```

Epicalc manipulates this matrix and gives rise to a display more understandable by most epidemiologists.

```
> logistic.display(glm0)
Logistic regression predicting diseased

               OR (95% CI)          P(Wald's test) P(LR-test)
eating eclair  23.75 (13.82,40.79)  < 0.001        < 0.001

Log-likelihood =  -527.6075
No. of observations =  977
AIC value = 1059.2
```

The odds ratio from the logistic regression is derived from exponentiation of the estimate, i.e. 23.75 is obtained from:

```
> exp(coef(summary(glm0))[2,1])
```

The 95% confidence interval of the odds ratio is obtained from

```
> exp(coef(summary(glm0))[2,1] + c(-1,1) * 1.96 *
  coef(summary(glm0))[2,2])
```

These values are close to simple calculation of the 2-by-2 table discussed earlier in Chapter 9. The log-likelihood and the AIC value will be discussed later.

The default values in *logistic.display* are 95% for the confidence intervals and the digits are shown to two decimal places. See the online help for details.

```
> args(logistic.display)
> help(logistic.display)
```

You can change the default values by adding the extra argument(s) in the command.

```
> logistic.display(glm0, alpha=0.01, decimal=2)
```

If the data frame has been specified in the glm command (using the 'data' argument), the output will show the variable description instead of the variable names. The P value from Wald's test is the same as that seen from the coefficient matrix obtained from

```
> coef(summary(glm0))
```

The output from logistic.display also contains the 'LR-test' result, which checks whether the likelihood of the given model, 'glm0', would be significantly different from the model without 'eclair.eat', which in this case would be the "null" model. For an independent variable with two levels, the LR-test does not add further important information because Wald's test has already tested the hypothesis. When the independent variable has more than two levels, the LR-test is more important than Wald's test as the following example demonstrates.

```
> glm1 <- glm(case ~ eclairgr, family=binomial, data=.data)
> logistic.display(glm1)

Logistic regression predicting diseased

                       OR(95%CI)            P(Wald's test) P(LR-test)
pieces of eclair eaten:                                    < 0.001
              ref.=0
   1                   17.57 (9.21,33.49)   < 0.001
   2                   22.27 (12.82,38.66)  < 0.001
   >2                  43.56 (22.89,82.91)  < 0.001

Log-likelihood =  -516.8236
No. of observations =  972
AIC value = 1041.6
```

Interpreting Wald's test alone, one would conclude that all levels of eclair eaten would be significant. However, this depends on the reference level. By default, **R** assumes that the first level of an independent factor is the referent level. If we relevel the reference level to be 2 pieces of eclair, Wald's test gives a different impression.

```
> eclairgr <- relevel(eclairgr, ref="2")
> pack()
> glm2 <- glm(case ~ eclairgr, family=binomial, data=.data)
> logistic.display(glm2)

Logistic regression predicting diseased

                      OR(95%CI)         P(Wald's test)  P(LR-test)
pieces of eclair eaten: ref.=2                          < 0.001
   0                  0.04 (0.03,0.08)  < 0.001
   1                  0.79 (0.52,1.21)  0.275
   >2                 1.96 (1.28,2.99)  0.002
======================================================================
```

The results show that eating only one piece of eclair does not reduce the risk significantly compared to eating two pieces.

While results from Wald's test depend on the reference level of the explanatory variable, the LR-test is concerned only with the contribution of the variable as a whole and ignores the reference level. We will return to this discussion in a later chapter.

Next, try 'saltegg' as the explanatory variable.

```
> glm3 <- glm(case ~ saltegg, family = binomial, data=.data)
> logistic.display(glm3)

Logistic regression predicting case

              OR (95% CI)       P(Wald's test)  P(LR-test)
saltegg:      2.54 (1.53,4.22)  < 0.001         < 0.001
     Yes vs No

Log-likelihood =  -736.998
No. of observations =  1089
AIC value = 1478
```

The odds ratio for 'saltegg' is statistically significant and similar to that seen from the cross-tabulation in Chapter 9. The number of valid records is also higher than the model containing 'eclairgr'.

Note:
One should always be careful when analysing data that contain missing values. Methods to handle missing values are beyond the scope of this book and for reasons of simplicity are ignored here. Readers are advised to deal with missing values properly prior to conducting their analysis.

To check whether the odds ratio is confounded by 'eclairgr', the two explanatory variables are put together in the next model.

```
> glm4 <- glm(case ~ eclairgr + saltegg, family=binomial)
> logistic.display(glm4, crude.p.value=TRUE)

Logistic regression predicting case

        crude OR(95%CI)  P value  adj. OR(95%CI)   P(Wald) P(LR-test)
eclairgr: ref.=2                                           < 0.001
  0     0.04 (0.03,0.08) < 0.001  0.04 (0.03,0.08) < 0.001
  1     0.79 (0.52,1.21) 0.275    0.79 (0.51,1.21)   0.279
  >2    1.96 (1.28,2.99) 0.002    1.96 (1.28,2.99)   0.002

saltegg: 2.37 (1.4,3.99) 0.001    1.01 (0.53,1.93)   0.975
  0.975
   Yes vs No

Log-likelihood =  -516.823
No. of observations =  972
AIC value = 1043.6
```

The odds ratios of the explanatory variables in '`glm4`' are adjusted for each other. The crude odds ratios are exactly the same as from the previous models with only single variable. The P value of 'saltegg' is shown as 0.001 due to rounding. In fact, it is 0.00112, which is not less than 0.001. Epicalc, for aesthetic reasons, displays P values as '`< 0.001`' whenever the original value is less than 0.001.

The adjusted odds ratios of 'eclairgr' do not change suggesting that it is not confounded by 'saltegg', whereas the odds ratio of 'saltegg' is celarly changed towards unity, and now has a very large P value. The difference between the adjusted odds ratio and the crude odds ratio is an indication that 'saltegg' is confounded by 'eclairgr', which is an independent risk factor. These adjusted odds ratios are close to those obtained from the Mantel-Haenszel method shown in chapter 9.

Now that we have a model containing two explanatory variables, we can compare models '`glm4`' and '`glm2`' using the *`lrtest`* command.

```
> lrtest(glm4, glm2)
Likelihood ratio test for MLE method
Chi-squared 1 d.f. =  0.0009809 , P value =  0.975
```

The P value of 0.975 is the same as that from 'P(LR-test)' of 'saltegg' obtained from the preceding command. The test determines whether removal of 'saltegg' in a model would make a significant difference than if it were kept. When there is more than one explanatory variable, 'P(LR-test)' from *`logistic.display`* is actually obtained from the *`lrtest`* command, which compares the current model against one in which the particular variable is removed, while keeping all remaining variables.

Logistic regression gives both the adjusted odds ratios simultaneously. The Mantel-Haenszel method only gives the odds ratio of the variable of main interest. An additional advantage is that logistic regression can handle multiple covariates simultaneously.

```
> glm5 <- glm(case~eclairgr+saltegg+sex, family=binomial)
> logistic.display(glm5)

Logistic regression predicting case

       crude OR(95%CI)    adj. OR(95%CI)    P(Wald's test) P(LR-test)
eclairgr: ref.=2                                           < 0.001
   0   0.04 (0.03,0.08)   0.04 (0.02,0.07)  < 0.001
   1   0.79 (0.52,1.21)   0.75 (0.49,1.16)  0.2
   >2  1.96 (1.28,2.99)   1.82 (1.19,2.8)   0.006

saltegg: 2.37 (1.41,3.99) 0.92 (0.48,1.76)  0.807          0.808
   Yes vs No
sex:     1.58 (1.19,2.08) 1.85 (1.35,2.53)  < 0.001        < 0.001
   Male vs Female

Log-likelihood =  -509.5181
No. of observations =  972
AIC value = 1031.0
```

The third explanatory variable 'sex' is another independent risk factor. Since females are the reference level, males have an increased odds of 90% compared to females. This variable is not a confounder to either of the preceding variables because it has not substantially changed the odds ratios of any of them (from '`glm4`'). The reason for not being able to confound is its lack of association with either of the preceding explanatory variables. In other words, males and females were not different in terms of eating eclairs and salted eggs.

Interaction

An interaction term consists of at least two variables, at least one of which must be categorical. If an interaction is present, the effect of one variable will depend on the status of the other and thus they are not independent. In **R** the interaction term can be specified in two ways: '`x1*x2`' or '`x1:x2`'. The former is equivalent to '`x1+ x2+x1:x2`'.

Examine the following model where the variables 'eclairgr' and 'beefcurry' are specified as an interaction term.

```
> glm6 <- glm(case ~ eclairgr*beefcurry, family=binomial)
> logistic.display(glm6, decimal=1)

Logistic regression predicting diseased

           crude OR(95%CI) adj. OR(95%CI) P(Wald's test) P(LR-test)
eclairgr: ref.=2                                         < 0.001
   0       0 (0,0.1)       0.1 (0,0.5)    0
   1       0.8 (0.5,1.2)   0.5 (0.1,2.5)  0.39
   >2      2 (1.3,3)       0.5 (0.1,3)    0.41

beefcurry: 2.7 (1.6,4.6)   1.4 (0.5,3.6)  0.53           < 0.001
   (Yes vs No)

eclairgr:beefcurry: ref.=2:No                            0.03
   0:Yes    -              0.3 (0.1,1.2)   0.09
   1:Yes    -              1.7 (0.3,9.7)   0.52
   >2:Yes   -              4.8 (0.7,33.9)  0.11

Log-likelihood =  -511.8
No. of observations =  972
AIC value = 1039.6
```

The last term, 'eclairgr:beefcurry', is the interaction term. Interpretation of the P values from Wald's test suggests that the interaction may not be significant. However, the P value from the LR-test is more important, in fact it is decisive. The value of 0.03 indicates that both 'eclairgr' and 'beefcurry' are not acting independently from each other. The crude odds ratios for the interaction terms are not applicable.

Readers may like to relevel the 'eclairgr' variable back to the original reference level (ref = "0") and compare the output.

```
> eclairgr <- relevel(eclairgr, ref="0")
> pack()
> glm7 <- glm(case~eclairgr*beefcurry, family=binomial,
  data=.data)
> logistic.display(glm7)
```

Stepwise selection of independent variables

The following section demonstrates stepwise selection of models in **R**.

First, a subset of the dataset is created to make sure that all the variables have valid (non missing) records. Note that the `glm` command also allows a subset of the dataset to be specified. Subsequent models use the 'eclair.eat' variable instead of 'eclairgr' in order to simplify the output.

```
> complete.data <- subset(.data, subset=!is.na(eclair.eat)
  & !is.na(beefcurry) & !is.na(saltegg) & !is.na(sex))

> glm8 <- glm(case ~ eclair.eat * beefcurry + saltegg + sex,
  family = binomial, data=complete.data)
```

The model may be too excessive. We let **R** select the model with lowest AIC.

```
> modelstep <- step(glm8, direction = "both")
Start:  AIC= 1038.5
 case ~ eclair.eat * beefcurry + saltegg + sex
                       Df Deviance   AIC
- saltegg               1     1026  1036
<none>                        1026  1038
- eclair.eat:beefcurry  1     1030  1040
- sex                   1     1039  1049

Step:  AIC= 1036.5
 case ~ eclair.eat + beefcurry + sex + eclair.eat:beefcurry
                       Df Deviance   AIC
<none>                        1026  1036
- eclair.eat:beefcurry  1     1030  1038
+ saltegg               1     1026  1038
- sex                   1     1039  1047
```

Initially, the AIC is 1038.5. The command `step` removes each independent variable and compares the degrees of freedom reduced, the new deviance and the new AIC. The results are increasingly sorted by AIC. The top one having the lowest AIC is the best one. At the first step, removal of 'saltegg' would give the lowest AIC and is therefore chosen and used for the next step.

In the second selection phase, not removing any remaining independent variable gives the lowest AIC. Thus the selection process stops with the remaining variables kept. Now, we check the results.

```
> summary(modelstep)
=================== Lines omitted ==================
Coefficients:
                        Estimate  St. Error z value Pr(>|z|)
(Intercept)               -2.672      0.494   -5.41  6.3e-08
eclair.eatTRUE             2.067      0.601    3.44  0.00059
beefcurry                 -0.903      0.573   -1.58  0.11484
sexMale                    0.586      0.163    3.59  0.00033
eclair.eatTRUE:beefcurry   1.412      0.685    2.06  0.03923
=================== Lines omitted ==================
```

The final model has 'saltegg' excluded. Sex is an independent risk factor. Eating eclairs is a risk factor, the effect of which was enhanced by eating beef curry. Eating beef curry by itself is a protective factor. However, when eaten with eclairs, the odds is increased and becomes positive.

It should be noted that stepwise regression is limited to exploration and often not suitable for specific hypothesis testing, the way most epidemiological studies are designed for. It tends to remove all non-significant independent variables from the model. In hypothesis testing one or a few independent variables are set for testing. The odds ratios and their confidence intervals must still be calculated regardless of the statistical significance.

Interpreting the odds ratio

Let's look more carefully at the final model.

```
> logistic.display(modelstep, crude=FALSE)

Logistic regression predicting case

                            adj. OR(95%CI)    P(Wald's)   LR-test
eclair.eat                  7.9 (2.43,25.66)  < 0.001     < 0.001
beefcurry: Yes vs No        0.4 (0.13,1.25)   0.115       < 0.001
sex: Male vs Female         1.8 (1.31,2.47)   < 0.001     < 0.001
eclair.eatTRUE:beefcurryYes 4.1 (1.07,15.71)  0.039       0.048

Log-likelihood =  -513.2296
No. of observations =  972
AIC value = 1036.5
```

All the three variables 'eclair.eat', 'beefcurry' and 'sex' are dichotomous. The odds ratio for 'sex' is that of males compared to females. For 'eclair.eat' it is TRUE vs FALSE and for 'beefcurry', "Yes" is compared to "No".

The independent variable 'sex' has an odds ratio of approximately 1.8, which means that males have approximately a 1.8 times higher risk than females. The other two variables, 'eclair.eat' and beefcurry, are interacting. The odds ratio of 'eclair.eat' depends on the value of 'beefcurry' and vice versa. Three terms 'eclair.eat', 'beefcurry' and their interaction term 'eclair.eat:beefcurry' need to be considered simultaneously.

If 'beefcurry' is "No" (did not eat beef curry), the 'eclair.eat:beefcurry' term is 0. The odds ratio for eclair.eat for this subgroup is therefore only 7.9. Among the beef curry eaters, the interaction term should be multiplied by 1 (since 'eclair.eat' and 'beefcurry' are both 1), the odds ratio is then 7.9 × 4.1 or approximately 32.4.

The required odds ratio can be obtained from computing the product of the appropriate odds ratio of the individual variables. However, the standard errors and 95% confidence interval cannot be easily computed from the above result.

A better way to get the odds ratio and 95% confidence interval for 'eclair.eat' among 'beefcurry' eaters is to relevel the variable and run the model again.

```
> complete.data$beefcurry <- relevel(complete.data$beefcurry,
  ref="Yes")
> glm9 <- glm(case ~ eclair.eat * beefcurry + sex,
  family = binomial, data = complete.data)

> logistic.display(glm9, crude=FALSE)

Logistic regression predicting case

                       adj. OR (95%CI)   P(Wald's test)  P(LR-test)
eclair.eat             32.4 (16.9,62.3)  < 0.001         < 0.001
beefcurry: No vs Yes   2.47 (0.8,7.59)     0.115         < 0.001
sex: Male vs Female    1.8  (1.31,2.47)  < 0.001         < 0.001
eclair.eatTRUE:        0.24 (0.06,0.93)    0.039           0.048
    beefcurryNo

Log-likelihood =  -513.2296
No. of observations =  972
AIC value = 1036.5
```

The odds ratio and 95% confidence interval of 'eclair.eat' among those who ate beef curry are in the first row because the 'beefcurry' term in the second row and the interaction term in the last row are both 0.

Other data formats

The above datasets are based on individual records. Sometimes, the regression is required to be performed based on an existing, aggregated table.

```
> zap()
> data(ANCtable)
> ANCtable
> use(ANCtable)
> death  <- factor(death)
> levels(death) <- c("no","yes")
> anc <- factor(anc)
> levels(anc) <- c("old","new")
> clinic <- factor(clinic)
> levels(clinic) <- c("A","B")
> pack()
```

The Epicalc function *`pack`* identifies all free vectors with the same length as the number of records in **`.data`** and adds them into the data.frame. These free vectors are then removed from the global environment.

```
> .data
  death anc clinic Freq
1    no old      A  176
2   yes old      A   12
3    no new      A  293
4   yes new      A   16
5    no old      B  197
6   yes old      B   34
7    no new      B   23
8   yes new      B    4
```

This is a format with 'Freq' being a variable denoting numbers of subjects in each category. This variable is put as the '`weight`' argument in the model.

```
> glm(death ~ anc+clinic, binomial, weight=Freq, data=.data)
```

The coefficients are the same as those from using the original dataset, **`ANCdata`**. However, the degrees of freedom is different.

Another data format for logistic regression is possible where the number of cases and number of controls of the same exposure are in the same row, but separate columns.

```
> .data$condition <- c(1,1,2,2,3,3,4,4)
> data2 <- reshape(.data, timevar="death", v.name="Freq",
  idvar="condition", direction="wide")
```

The variable 'condition' is created to facilitate reshaping. The reshaped data, `data2` has only four rows of data compared to **`.data`**, which has 8 rows.

```
> data2
  anc clinic condition Freq.no Freq.yes
1 old      A         1     176       12
3 new      A         2     293       16
5 old      B         3     197       34
7 new      B         4      23        4
```

The first column in each row is the 'row.names' of the data frame. This data frame can be written to a text file with 'row.names' and the variable 'condition' (the third variable) omitted.

Logistic regression for '`data2`' can be carried out as follows:

```
> glm(cbind(Freq.yes, Freq.no) ~ anc + clinic, data=data2,
   family=binomial)
```

The left-hand side of the formula is a result of column binding the two outcome frequency columns. The remaining parts of the commands remain the same as for the case-by-case format. The coefficients and standard errors from this command are the same as those above. However, the residual deviance and AIC are much smaller due to the smaller number of degrees of freedom.

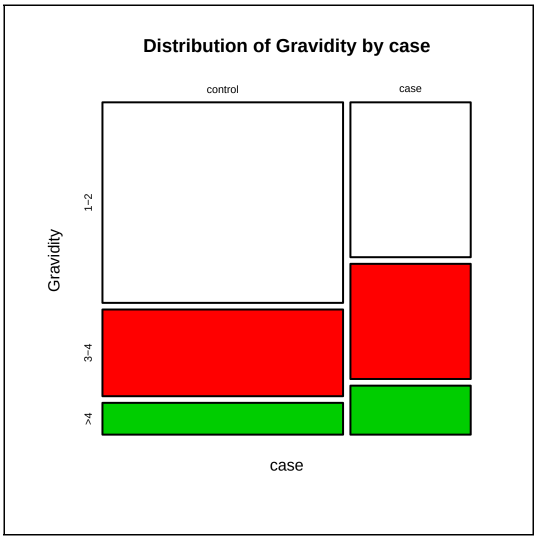
Case-by-case format of data is most commonly dealt with in the actual data analysis. The formats in **`ANCtable`** and '`data2`', which are occasionally found, are mainly of theoretical interest.

More than 2 strata

The dataset **`Ectopic`** comes from a case-control study testing a hypothesis whether previous induced abortion is a risk factor for current ectopic pregnancy. There were three groups of patients studied: ectopic pregnancy patients ('EP'), current clients who came for an induced abortion ('IA') and those who came for delivery ('deli'). For simplicity, at this stage, the latter two groups are combined and classed as the controls whereas the first group is classed as the cases. The exposure of interest is 'hia' or history of previous induced abortion and a potential confounder is 'gravi' or level of gravidity. Try the following commands in **R**:

```
> zap()
> data(Ectopic)
> use(Ectopic)
> des()

  No. of observations = 723
  Variable     Class       Description
1 id           integer
2 outc         factor      Outcome
3 hia          factor      Previous induced abortion
4 gravi        factor      Gravidity

> summ()
```

```
No. of observations = 723

  Var. name Obs.   mean   median  s.d.   min.   max.
1 id        723    362    362     208.86 1      723
2 outc      723    2      2       0.817  1      3
3 hia       723    1.545  2       0.498  1      2
4 gravi     723    1.537  1       0.696  1      3

> tab1(outc, graph=F)
> tab1(hia, graph=F)
> tab1(gravi, graph=F)
> case <- outc == "EP"
> case <- factor(case)
> levels(case) <- c("control","case")
> tabpct(case, gravi)
```

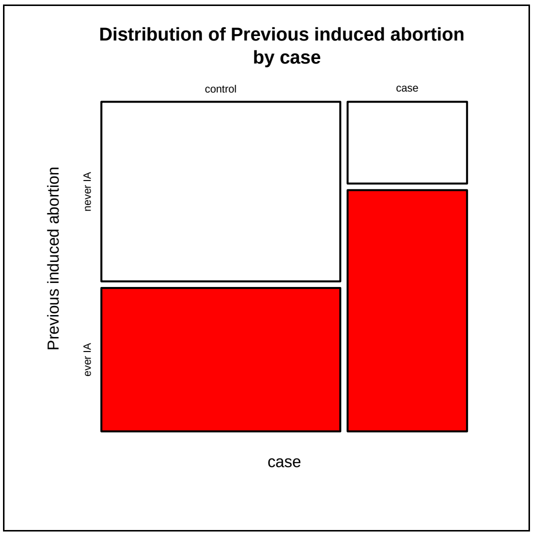


The cases had a higher level of gravidity.

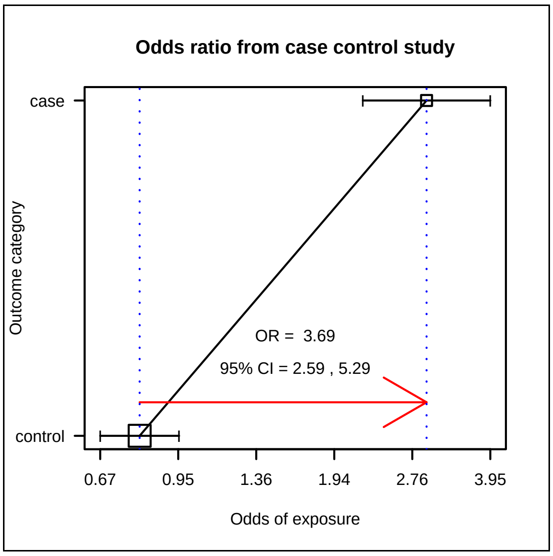
```
> tabpct(case, hia) -> case.hia
```

The above command will show only the graph, since we have saved the output to an object. Inspection of this object can be done by simply typing the object's name.

The cases also had a higher experience of induced abortion.



```
> cc(case, hia, design = "case-control")

         hia
case       no yes Total
  control 268 214   482
  case     61 180   241
  Total   329 394   723

OR =  3.689
95% CI = 2.595 5.291
Chi-squared = 59.446 ,  1 d.f. , P value = 0
Fisher's exact test (2-sided) P value = 0
```

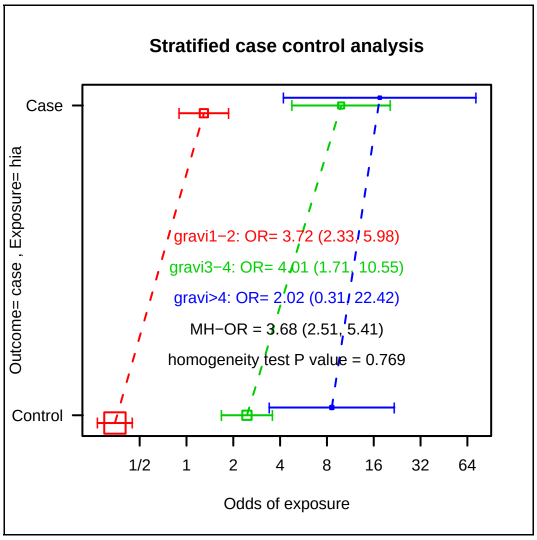


This graph is specified with 'design' = "case-control", therefore the orientation of it is adjusted toward the outcome variable. The odds of exposure among the cases are on the right (higher value).

Next we adjust for gravidity.

```
> mhor(case, hia, gravi, design="case-control")

Stratified analysis by  gravi
               OR lower lim. upper lim.  P value
gravi 1-2    3.72      2.328       5.98 6.26e-09
gravi 3-4    4.01      1.714      10.55 3.52e-04
gravi >4     2.02      0.307      22.42 4.62e-01
M-H combined 3.68      2.509       5.41 6.12e-12

M-H Chi2(1) = 47.29 , P value = 0
Homogeneity test, chi-squared 2 d.f. = 0.52 , P value = 0.769
```

The stratified analysis shows output tables for the three strata of gravidity and corresponding three exposure lines in the graph. The odds of exposure to induced abortion increases (moving towards the right-hand side) with gravidity. The odds among the control group is lower (more on the left) in each stratum of the gravidity group. The slopes of the three lines are somewhat similar indicating minimal interaction, and this is supported by the P value from the homogeneity test. The MH combined odds ratio is similar to the crude odds ratio indicating rather little effect of confounding by gravidity.



For logistic regression we can use the `glm` function, as before.

```
> glm1 <- glm(case ~ hia, family = binomial)
```

Similar to the preceding section, *logistic.display* can be used in order to obtain the odds ratio and 95% confidence interval of the exposure to induced abortion.

```
> logistic.display(glm1)

Logistic regression predicting case : case vs control

                   OR(95%CI)       P(Wald's test) P(LR-test)
hia:               3.7 (2.63,5.2)  < 0.001        < 0.001
  ever IA vs never IA

Log-likelihood =  -429.3863
No. of observations =  723
AIC value = 862.77

> glm2 <- glm(case ~ hia + gravi, binomial)
> logistic.display(glm2)

Logistic regression predicting case : case vs control

          crude OR(95%CI)  adj. OR(95%CI)  P(Wald's test)  P(LR-test)
hia:      3.7 (2.6,5.2)    3.7 (2.5,5.4)   < 0.001         < 0.001
  ever IA vs never IA

gravi: ref.=1-2                                            1
  3-4     1.7 (1.2,2.4)    1.0 (0.7,1.5)   0.989
  >4      2.0 (1.2,3.2)    1.0 (0.6,1.7)   0.992

Log-likelihood =  -429.3861
No. of observations =  723
AIC value = 866.77
```

The AIC from 'glm1' is lower than the one from 'glm2' indicating a better fit. Cases of ectopic pregnancies had approximately 3.7 times the odds of previous exposure to induced abortion compared to the control group. Gravidity has no effect on the outcome and is not a confounder.

References

Hosmer Jr DW & Lemeshow S (2004). Applied Logistic Regression, 2nd Edition.

Kleinbaum DG & Klein M. Logistic Regression. A self-learning Text (2nd Edition). Springer-Verlag New York, Inc. August 2002.

Exercises

Problem 1.

With the data frame '`complete.data`', compute the odds ratio and 95% confidence interval for combined exposure to 'eclair.eat' and 'beefcurry' using the group who were exposed to neither eclair nor beef curry as the referent group.

Problem 2.

Use the **`ANCtable`** dataset and the function xtabs to create a stratified 2x2 table. Then use the *mhor* function to analyse the adjusted odds ratio.

Hint: '`help(xtabs)`', '`help(mhor)`'.

Problem 3.

Use the **`Hakimi`** dataset to do a similar analysis.

Problem 4.

In the **`Ectopic`** dataset, unclass 'gravi' and use logistic regression to investigate a dose response relationship (linear trend) between gravidity and risk of ectopic pregnancy, after adjustment for the effect of previous induced abortion ('hia').

Chapter 16: Matched Case Control Study

Examples in previous chapters have cases and control independently recruited. For a matched case control study, when a case is recruited, a control, or a set of controls (more than one person), can be selected to match with the case in some parameters such as age and sex and other conditions such as being siblings or neighbours. If control series are chosen based on matching on only age and sex and the purpose of such selection is only to avoid imbalances, then the dataset should probably be analysed in a non-matched setting. There are many good books on how to analyse case-control studies, particularly in the matched setting, and readers should consult the references at the end of this chapter.

The examples in this chapter are for demonstration purposes only. The sample size is rather small for making solid conclusions. However, the methods can still be applied to other matched case-control studies.

In the analysis of matched sets, comparison is made within each matched set rather than one series against the other. In this chapter, the datasets **`VC1to1`** and **`VC1to6`** consist of data from a matched case-control study testing whether smoking, drinking alcohol and working in the rubber industry are risk factors for oesophageal cancer. Each case was matched with his/her neighbours of the same sex and age group. The matching ratio varied from 1:1 to 1:6. The file **`VC1to6`** is the full dataset whereas **`VC1to1`** has the number of controls per case reduced to 1 for all matched sets. This latter file is first used for matched pair analysis.

```
> zap()
> data(VC1to1)
> use(VC1to1)
> des()

No. of observations = 52
  Variable      Class           Description
1 matset        numeric
2 case          numeric
3 smoking       numeric
4 rubber        numeric
5 alcohol       numeric
```

```
> summ()
No. of observations = 52

  Var. name obs.   mean   median  s.d.   min.   max.
1 matset    52     13.5   13.5    7.57   1      26
2 case      52     0.5    0.5     0.5    0      1
3 smoking   52     0.81   1       0.4    0      1
4 rubber    52     0.33   0       0.47   0      1
5 alcohol   52     0.52   1       0.5    0      1

> head(.data)
  matset case smoking rubber alcohol
1      1    1       1      0       0
2      1    0       1      0       0
3      2    1       1      0       1
4      2    0       1      1       0
5      3    1       1      1       0
6      3    0       1      1       0
```

There are 26 matched pairs as shown in the sorted 'matset' variable. The codes of the variable 'case' are 1 for diseased and 0 for non-diseased. We now reshape the data to facilitate data exploration.

```
> wide <- reshape(.data, timevar="case", v.names=c("smoking",
   "rubber", "alcohol"), idvar="matset", direction="wide")

> head(wide,3)
matset smoking.1 rubber.1 alcohol.1 smoking.0 rubber.0 alcohol.0
1      1         1        0         0         1        0
3      2         1        0         1         1        1
5      3         1        1         0         1        1
```

The original data frame `.data` has the variables arranged in *long* form. Each record represents one subject. The new data frame '`wide`' is in *wide* form. Each record represents one matched pair. Cross-tabulating the smoking habit of cases and controls in each matched pair can now be done easily.

```
> attach(wide)
> table(smoking.1, smoking.0, dnn=c("smoking in case",
    "smoking in control"))
               smoking in control
smoking in case  0  1
              0  0  5
              1  5 16
```

The optional argument 'dnn' in the above `table` command allows the dimension names to be specified, facilitating interpretation. From this cross tabulation, there was no matched pair where both the case and control were non-smokers. There were sixteen matched pairs where both were smokers. In five pairs, the cases smoked but the controls did not (left lower corner). In the remaining five pairs (right upper corner), the controls smoked while the cases did not.

The level of contrast of history of smoking between the two based on matched pairs is called a conditional odds ratio. It is the value of the left lower corner cell divided by the right upper corner cell. In this case the conditional odds ratio (sometimes called McNemar's odds ratio) is 5/5 = 1. In fact, this means that the ratio of discordant counts between cases having the exposure against controls having exposure is 1.

Epicalc has a function *`matchTab`* that can be used to analyse the matched set (not necessary 1 case per 1 control) from the original dataset as follows:

```
> detach(wide)
> matchTab(case, smoking, strata=matset)

Number of controls = 1
                    No. of controls exposed
No. of cases exposed 0  1
                   0 0  5
                   1 5 16

Odds ratio by Mantel-Haenszel method = 1

Odds ratio by maximum likelihood estimate (MLE) method = 1
 95%CI= 0.29 , 3.454
```

The two methods give the same values for the odds ratio. The MLE method also gives a 95% confidence interval of the estimate.

1:n matching

If there is no serious problem on scarcity of diseased cases, the best ratio of matching is one case per control. Resources spent on collecting data from each individual will be most efficient regardless of whether the subject is a case or a control. However, when the disease of interest is rare, it is often cost-effective to increase the number of controls per case. The efficiency (especially resources spent on collecting data from extra controls) is decreased but it means that the study may end sooner.

We now analyse the full dataset, where each case may have between 1 and 6 matched controls.

```
> zap()
> data(VC1to6); use(VC1to6)
> des()
> summ()

No. of observations = 119

================ lines omitted ============
> .data
    matset case smoking rubber alcohol
```

```
1        1    1       1      0       0
2        1    0       1      0       0
3        2    1       1      0       1
4        2    0       1      1       0
================= lines omitted ============
116     26    0       0      0       0
117     26    0       1      1       0
118     26    0       0      0       0
119     26    0       1      1       1
```

It would be very cumbersome to reshape this data into a wide form. Let's use the *Epicalc* function `matchTab` instead.

```
> matchTab(case, smoking, strata=matset)

Number of controls = 1
                    No. of controls exposed
No. of cases exposed 0 1
                   0 0 0
                   1 0 3

Number of controls = 2
                    No. of controls exposed
No. of cases exposed 0 1 2
                   0 0 0 1
                   1 1 1 0
================= lines omitted ============
Number of controls = 6
                    No. of controls exposed
No. of cases exposed 0 1 2 3 4 5 6
                   0 0 0 0 1 0 0 0
                   1 0 0 0 0 0 1 2

Odds ratio by Mantel-Haenszel method = 1.988

Odds ratio by maximum likelihood estimate (MLE) method = 2.066
 95%CI= 0.678 , 6.299
```

The command gives six tables based on the matched sets of the same size (cases per controls). The last table, for example, shows that there are four matched sets with six controls per case. One of them has case non-exposed and three out of the controls exposed. One has case exposed and five of the six controls non-exposed. The remaining two sets have the case and all of the six controls exposed. The odds ratios from the two different datasets are slightly different. However, the effect of smoking on the outcome is still not statistically significant as the 95% confidence interval of the odds ratio contains the value 1.

Logistic regression for 1:1 matching

As discussed above, the conditional odds ratio for the 1:1 matched case-control study is based on the ratio of discordant exposures between cases and controls of the same matched pair. From the modelling point of view, the difference of outcome within the matched set is determined by the difference of exposure between the case and the control. The former difference is fixed at one because the outcome of a case is equal to 1 and the outcome of a control is equal to 0. The exposure difference is computed within the matched set.

```
> zap()
> data(VC1to1);  use(VC1to1)
> use(wide)
> smoke.diff <- smoking.1 - smoking.0
> alcohol.diff <- alcohol.1 - alcohol.0
> rubber.diff <- rubber.1 - rubber.0
> outcome.1 <- rep(1, 26) # 26 cases with outcome being 1
> outcome.0 <- rep(0, 26) # 26 controls with outcome being 0
> outcome.diff <- outcome.1 - outcome.0
> cbind(outcome.diff, smoke.diff, alcohol.diff)
> pack()
> summ()
No. of observations = 26

   Var. name    obs. mean   median  s.d.   min.   max.
1  matset       26   13.5   13.5    7.65   1      26
2  smoking.1    26   0.81   1       0.4    0      1
3  rubber.1     26   0.31   0       0.47   0      1
4  alcohol.1    26   0.65   1       0.49   0      1
5  smoking.0    26   0.81   1       0.4    0      1
6  rubber.0     26   0.35   0       0.49   0      1
7  alcohol.0    26   0.38   0       0.5    0      1
8  alcohol.diff 26   0.27   0       0.6    -1     1
9  outcome.0    26   0      0       0      0      0
10 outcome.1    26   1      1       0      1      1
11 outcome.diff 26   1      1       0      1      1
12 rubber.diff  26   -0.04  0       0.6    -1     1
13 smoking.diff 26   0      0       0.63   -1     1
```

Note that the variable 'outcome.diff' is 1 throughout all records because the outcome for case is 1 and for control is 0 whereas difference in exposure to alchohol, rubber and smoking can be 1 (case exposed control not exposed), 0 (either both case and control exposed or none of them exposed) and -1 (case not exposed but control exposed).

Now we perform logistic regression predicting difference of outcome from difference in smoking history.

```
> co.lr1 <- glm(outcome.diff ~ smoke.diff-1, binomial)
> summary(co.lr1)

Call:
glm(formula = outcome.diff ~ smoke.diff-1, family=binomial)
Coefficients:
           Estimate Std. Error z value Pr(>|z|)
smoke.diff    0.000      0.632       0        1

(Dispersion parameter for binomial family taken to be 1)
```

```
    Null deviance: 36.044  on 26  degrees of freedom
Residual deviance: 36.044  on 25  degrees of freedom
AIC: 38.04
```

In the above glm model, the difference of the outcome (which is always 1 for the above reason) is predicted by the difference in smoking habit. There is an additional term '-1' in the right-hand side of the formula, which indicates that the intercept should be removed from the model. Usually, the intercept is the expected value of the dependent variable (the variable on the left-hand side of the formula) when all the independent variables are equal to 0. In conditional logistic regression, there is no such intercept because the difference of the outcome is fixed to 1, the logit of which is 0.

With the coefficient of 0, the odds ratio is exp(0) = 1, which is the same as the result from the matched tabulation. The 95% confidence interval of the odds ratio can be obtained from:

```
> exp(confint.default(co.lr1))
            2.5 % 97.5 %
smoke.diff 0.2895 3.4542
```

These values are exactly the same as those obtained from the matched tabulation. Epicalc can display the results in a more convenient format.

```
> logistic.display(co.lr1)
Logistic regression predicting outcome.diff

                  OR(95%CI)      P(Wald's test) P(LR-test)
smoke.diff        1 (0.29,3.45)  1              -

Log-likelihood = -18.0218
No. of observations = 26
AIC value = 38.0437
```

Recall that the advantage of logistic regression is in its ability to handle more than one exposure variable. Run a logistic model again, adding the alcohol term.

```
> co.lr2 <- glm(outcome.diff ~ smoke.diff + alcohol.diff-1, binomial)
> logistic.display(co.lr2, decimal=1)

Logistic regression predicting outcome.diff

              crude OR(95%CI) adj.OR(95%CI)  P(Wald's)  P(LR-test)
smoke.diff    1 (0.3,3.5)     0.7 (0.2,2.9)  0.66       0.66
alcohol.diff  4.5 (1,20.8)    4.8 (1,23.2)   0.05       0.03

Log-likelihood = -15.513
No. of observations = 26
AIC value = 35.026
```

The introduction of 'alcohol.diff' has changed the coefficient of 'smoke.diff' substantially indicating that smoking is confounded by drinking alcohol.

Conditional logistic regression

The above logistic regression analysis, which is based on manipulating the data, is still rather cumbersome. The statistical analyst needs to reshape the dataset, and create the values of difference in the outcome and exposure variables. Moreover, the method is applicable only for 1:1 matching.

A simpler method of multivariate analysis of the **VC1to1** dataset is to use the command `clogit` (short for 'conditional logit') from the **survival** package. The original dataset in long format can be used.

```
> zap()
> library(survival)
> use(.data)
> clogit1 <- clogit(case ~ smoking+alcohol+strata(matset))
> summary(clogit1)

  n= 52
          coef exp(coef) se(coef)      z    p
smoking -0.314      0.73    0.708 -0.444 0.66
alcohol  1.572      4.81    0.803  1.957 0.05

        exp(coef) exp(-coef) lower .95 upper .95
smoking      0.73      1.369     0.182      2.92
alcohol      4.81      0.208     0.998     23.23
Rsquare= 0.092   (max possible= 0.5 )
Likelihood ratio test= 5.02  on 2 df,   p=0.0814
Wald test            = 3.83  on 2 df,   p=0.147
Score (logrank) test = 4.62  on 2 df,   p=0.0991
```

The top section of the results reports that the clogit command actually calls another generic command `coxph`. If the called command is used, the result will be the same.

```
> coxph(formula = Surv(rep(1, 52), case) ~ smoking + alcohol +
  strata(matset), method = "exact")
```

The odds ratios and their 95% confidence intervals from `clogit` are the same as those obtained by modelling the difference. The last section contains several test results, each of which indicates that the model is not significantly different from the null model (the model that does not include any predictor variables).

The Epicalc function *`clogistic.display`* can be used to obtain a nicer output.

```
> clogistic.display(clogit1)

Conditional logistic regression predicting case : 1 vs 0

                 crude OR(95%CI)   adj. OR(95%CI)    P(Wald)  P(LR)
smoking: 1 vs 0  1.0 (0.29, 3.45)  0.73 (0.18,2.92)  0.66     0.655
alcohol: 1 vs 0  4.5 (0.97,20.83)  4.81 (1,23.23)    0.05     0.025

No. of observations =  52
```

References

Breslow NE, Day NE (1980). The Analysis of Case-Control Studies (Statistical Methods in Cancer Research, Vol. 1). Int Agency for Research on Cancer.

Exercises

Problem 1.
Carry out a matched tabulation for alcohol exposure in **`VC1to6`**. Compare the results with those obtained from the conditional logistic regression analysis.

Problem 2.
Refer to the log likelihood and AIC values in the preceding chapter on generalized linear model.

The conditional logistic regression model gives neither the log likelihood nor AIC value but it does give the conditional log likelihood, which also indicates the level of fit. This conditional log likelihood can be used for comparison of nested models from the same dataset.

```
> clogit3 <- clogit(case ~ smoking + alcohol +rubber + strata(matset))
> attributes(clogit3)
> clogit3$loglik
[1] -37.89489 -31.89398
```

The element 'loglik' from each `clogit` command (analogous to 'logLik' of `glm`) contains two sub-elements. The first sub-element, which is the conditional likelihood of the null model, is the same for all the conditional logistic regression models. The second sub-element is specific to the particular model. Twice the absolute difference of the two sub-elements is equal to the likelihood ratio test for the model. This test result can be seen from the display of the model.

Try different models and compare their conditional log likelihoods. Choose the best fitting model.

Chapter 17: Polytomous Logistic Regression

Logistic regression is well known for the modelling of binary outcomes. In some occasions, the outcome can have more than two non-ordered categories.

In chapter 15 we looked at the **`Ectopic`** dataset, which came from a study testing a hypothesis whether previous induced abortion is a risk factor for current ectopic pregnancy (EP). The outcome has two groups of controls: subjects coming for induced abortion services (IA) and women who delivered babies (Deli). Both groups were used to represent intra-uterine pregnancy. The outcome in this study has therefore three nominal categories.

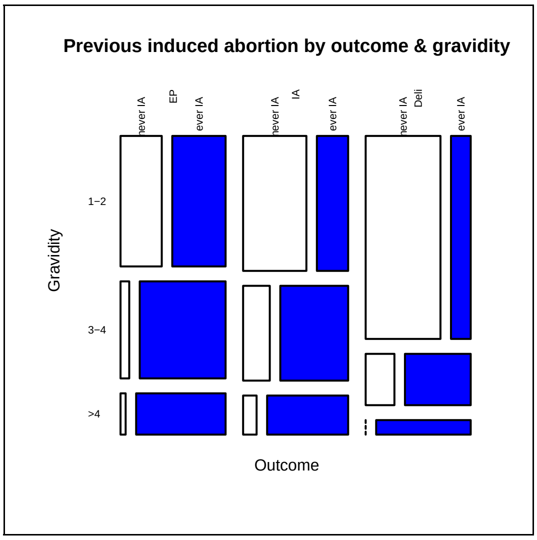
Tabulation

```
> zap()
> data(Ectopic);  use(Ectopic)
> des()
No. of observations =723
  Variable      Class           Description
1 id            integer
2 outc          factor          Outcome
3 hia           factor          Previous induced abortion
4 gravi         factor          Gravidity

> tabpct(outc, hia, graph=FALSE)
Original table
       Previous induced abortion
Outcome  never IA  ever IA  Total
  EP           61      180    241
  IA          110      131    241
  Deli        158       83    241
  Total       329      394    723

Row percent
       Previous induced abortion
Outcome  never IA  ever IA  Total
   EP          61      180    241
           (25.3)   (74.7)  (100)
   IA         110      131    241
           (45.6)   (54.4)  (100)
   Deli       158       83    241
           (65.6)   (34.4)  (100)
```

```
Column percent
       Previous induced abortion
Outcome  never IA       %  ever IA       %
  EP           61  (18.5)      180  (45.7)
  IA          110  (33.4)      131  (33.2)
  Deli        158  (48.0)       83  (21.1)
  Total       329   (100)      394   (100)
```

Two-way tabulation reveals the highest proportion (74.7%) of ever IA in the EP group compared to 54.4% and 34.4% in the IA and Deli groups, respectively.

```
> table1 <- table(outc, gravi, hia)
> plot(table1, col=c("white", "blue"), las=4, main="Previous
   induced abortion by outcome & gravidity", xlab="Outcome",
   ylab= "Gravidity")
```



The mosaic plot gives complicated information. The column of the plot is outcome, which is divided into EP, IA and Deli, as previously described. The sizes of the 3 “columns” are the same (241 subjects). Each row represents the three levels of gravidity (number of pregnancies): 1-2, 3-4 and > 4, respectively. The distribution of gravidity among the EP and IA groups are more or less the same, i.e. around a half having 1-2 pregancies, whereas among the women coming to deliver a baby, the percentage in this group is much higher (about 75%). Finally, information can be obtained from the different colours. Blue areas represent women who experienced previous induced abortion while white represents those who did not. In each column, such a percentage appears to increase with gravidity, i.e. women who have high gravidity will have a higher level of exposure to induced abortion in the past. Comparison among the three columns, which is the main hypothesis of this study, shows that the proportion of blue colour is highest among the EP group.

Polytomous logistic regression using R

Polytomous logistic regression, sometimes called multinomial logistic regression, is used when the outcome contains more than two categories. In this case, the codes for the outcome are: 1 = EP, 2=IA and 3=Deli. The command for such regression is contained in the 'nnet' package, the package based on neural network concepts.

```
> library(nnet)
> multi1 <- multinom(outc ~ hia); multi1
# weights:  9 (4 variable)
initial  value 794.296685
final  value 753.732244
converged
Call:
multinom(formula = outc ~ hia)

Coefficients:
     (Intercept) hiaever IA
IA       0.58958   -0.90735
Deli     0.95170   -1.72585

Residual Deviance: 1507.5
AIC: 1515.5
```

The upper part of the output concerns the iteration process of the neural network. The important part for epidemiology is in the 'Coefficients:' section. Interpretation of the coefficients of polytomous logistic regression is rather complicated, especially when the design has one group of cases and more than one group of controls.

There are three outcome categories. The first one, 'EP', is the reference against which the two comparisons are made. The risk for being EP in this case is reverted to the chance of not being EP within the dataset. Since this study was a case control study, the intercept values should be ignored. The most important part is the coefficients of 'hia'.

For those who had a history of induced abortion, the logit of being IA in this pregnancy changes by -0.90735 unit. This is equivalent to an odds ratio of exp(-0.90735) or 0.403.

"The odds of having intra-uterine pregnancy (and eventually came for induced abortion) is reduced by a factor of 0.403 if the subject had a history of induced abortion" can be rephrased as "The odds of having ectopic pregnancy (and therefore not in the IA group) is increased by 1/0.403, or a factor of 2.48".

Similarly, the odds ratio for EP using Deli as the control is 1 / $e^{-1.7258539}$ = 5.617.

It is worth remembering that in the chapter on logistic regression, the odds ratio for history of previous induced abortion using two groups combined was obtained as follows:

```
> logistic.display(glm(outc=="EP" ~ hia, binomial))
Logistic regression predicting outc == "EP"

                          OR(95%CI)       P(Wald's test) P(LR-test)
hia: ever IA vs never IA  3.7 (2.63,5.2)  < 0.001        < 0.001

Log-likelihood = -429.3863
No. of observations = 723
AIC value = 862.772
```

The odds ratio from the logistic regression in chapter 15 of 3.695 is between the two odds ratios computed from polytomous logistic regression in this chapter.

Standard errors can be obtained by the following command:

```
> summary(multi1) -> s1; s1
========== coefficient section omitted =============
Std. Errors:
     (Intercept) hiaever IA
IA       0.15964    0.19666
Deli     0.15074    0.20081
========== correlation section omitted ============
```

Only the standard errors section is displayed because the coefficients section is shown above with the previous command and the correlation section is not directly related here.

To obtain the z value for each cell, type:

```
> coef(s1) / s1$st -> z; z
     (Intercept) hiaever IA
IA        3.6932    -4.6139
Deli      6.3136    -8.5943
```

High levels of 'z' indicate the coefficient is several times the value of the standard error. In other words, the coefficient is far away from 0, which the null hypothesis (of no association) is based on. P values can be further obtained by:

```
> pnorm(abs(z), lower.tail=FALSE)*2 -> p.values
> p.values
     (Intercept) hiaever IA
IA    2.2143e-04 3.9513e-06
Deli  2.7264e-10 8.3774e-18
```

Note that the absolute values of 'z' were used before computing the P values.

The 95% confidence interval of the coefficients can be computed based on the coefficients and the standard errors.

```
> coeff.lower.95ci <- coef(s1) - qnorm(.975) * s1$st
> coeff.lower.95ci
> coeff.upper.95ci <- coef(s1) + qnorm(.975) * s1$st
> coeff.upper.95ci
```

The odds ratios and their 95% confidence intervals can be achieved from exponentiation of the coefficients and their upper and lower 95% CI.

Display of polytomous regression results

The above computing process is quite cumbersome. To simplify the amount of typing and to obtain a tidy output of results, `mlogit.display` from *Epicalc* can be used on the model summary.

```
> mlogit.display(multi1)

Outcome =outc; Referent group = EP
            IA
            Coeff./SE       RRR(95%CI)
(Intercept)  0.59/0.16***     -
hiaever IA  -0.91/0.197***  0.404(0.275,0.593)

            Deli
            Coeff./SE       RRR(95%CI)
(Intercept)  0.95/0.151***    -
hiaever IA  -1.73/0.201***  0.178(0.12,0.264)

Residual Deviance: 1507.464
AIC = 1515.464
```

The formatting of the output has been modified to fit on the page. The P values are coded with the number of asterisks conforming to those used in the summary of the 'glm' and 'lm' models. Odds ratios for the intercepts are irrelevant and are therefore omitted. As discussed previously, the odds ratios here are not for risk of ectopic pregnancy but for their reciprocals.

To include the variable 'gravi' in the model, type:

```
> multi2 <- multinom(outc ~ hia + gravi)
> mlogit.display(multi2)
```

Optionally, the upper three commands can be combined and replaced with the one below, which gives the same results.

```
> mlogit.display(multinom(outc ~ hia + gravi))
# weights:  15 (8 variable)
initial  value 794.296685
iter  10 value 744.763718
final  value 744.587307
converged

Outcome =outc; Referent group = EP
```

```
            IA
            Coeff./SE       RRR(95%CI)
(Intercept)  0.51/0.165**    -
hiaever IA  -1.11/0.223***  0.33(0.213,0.511)
gravi3-4     0.39/0.224     1.472(0.95,2.283)
gravi>4      0.47/0.295     1.599(0.897,2.85)

            Deli
            Coeff./SE       RRR(95%CI)
(Intercept)  1.02/0.154***  -
hiaever IA  -1.49/0.222***  0.225(0.146,0.348)
gravi3-4    -0.47/0.24      0.628(0.392,1.004)
gravi>4     -0.7/0.366      0.499(0.243,1.022)

Residual Deviance: 1489.175
AIC = 1505.175
```

Again, the formatting of the output has been modified to fit on the page. None of the coefficients and odds ratios of gravidity in this model are significant. However, this model has a much lower residual deviance compared to model '`multi1`'. A reduction from 1507.464 to 1489.175 or 18.289 units at a cost of introducing four more parameters (two gravidity levels for two outcomes) can be considered worthwhile since the P value from the chi-squared of 18.289 with 4 degrees of freedom is 0.001. Moreover, the AIC value from model '`multi2`' of 1505.175 is obviously smaller than that from '`multi1`' of 1515.464.

For the final conclusion, after adjustment for gravidity, history of previous induced abortion significantly increases the risk for ectopic pregnancy. The odds ratio is 1/.33 or 3.03 if the client currently requesting for induced abortion is used as the referent group and 1/.225 or 4.4 if women who delivered a baby is the referent group. It is well known that induced abortion is often repeated. Current clients for this service usually experience more induced abortions than the general population. Ectopic pregnancy patients have even more experience of induced abortion than this group. Therefore, history of induced abortion is very likely a true risk factor for ectopic pregnancy.

Selection of referent outcome group

The outcome variable in a polytomous logistic regression is usually a factor containing more than two levels. The first level is usually taken as the referent level. The same results of the analysis could be obtained by creating three dummy outcome variables and using them in a matrix format with the `cbind` function.

```
> ep <- outc == "EP"
> ia <- outc == "IA"
> deli <- outc == "Deli"
> multi3 <- multinom(cbind(ep,ia,deli) ~ hia+gravi)
> summary(multi3)

> mlogit.display(multi3)
```

The above commands should give the same results as those from 'multi2' except that the names of outcome groups are in lower case.

Since the first column is always used as the referent group, one can exploit this method to shuffle the order of outcome variables in order to change the referent group. For example, to use 'deli' as the referent level, 'deli' is put as the first column of the outcome matrix:

```
> multi4 <- multinom(cbind(deli,ep,ia) ~ hia+gravi)
> mlogit.display(multi4)

Outcome =cbind(deli, ep, ia); Referent group = deli

            ep
            Coeff./SE       RRR(95%CI)
(Intercept) -1.02/0.154***  -
hiaever IA   1.49/0.222***   4.443(2.877,6.861)
gravi3-4     0.47/0.24       1.593(0.996,2.55)
gravi>4      0.7/0.366       2.005(0.979,4.107)

            ia
            Coeff./SE       RRR(95%CI)
(Intercept) -0.51/0.131***  -
hiaever IA   0.38/0.215      1.466(0.963,2.233)
gravi3-4     0.85/0.237***   2.346(1.475,3.732)
gravi>4      1.16/0.369**    3.205(1.554,6.607)
```

The output is relatively easy to interpret. Using delivery as the referent outcome, for a woman with a history of induced abortion, the odds of being 'EP' or having an ectopic pregnancy in this admission increased by 4.443 fold (which is highly significant) and that for being a (repeating) induced abortion patient increased by only 47 percent (OR = 1.466, which is non-significant). On the other hand, increasing gravidity does not independently increase the risk for ectopic pregnancy but significantly, and in a dose-response relationship fashion, increases the chance for being a client for induced abortion service in the current visit.

Exercises

In a fictitious trial of a vaccine on 120 mice, 75 were given the vaccine ('vac' = 1) while 45 were given a placebo ('vac' = 0). Among these were 35 young mice ('agegr' = 0) and 85 old mice ('agegr' = 1).

There were three levels of outcomes: 1 = no change, 2 = became immune, 3 = died.

Outcome	vac	agegr	total
1	0	0	25
1	0	1	15
1	1	0	4
1	1	1	8
2	0	0	1
2	0	1	0
2	1	0	25
2	1	1	35
3	0	0	3
3	0	1	1
3	1	0	2
3	1	1	1

Problem 1.

Is there any difference in age group among the two groups of these vaccine recipients?

Problem 2.

Is there any association between age group and outcome?

Problem 3.

Is there any difference in outcomes between the vaccine and placebo treatment groups?

Chapter 18: Ordinal Logistic Regression

In the previous chapters, all variables that were factors were treated as non-ordered categorical variables. Polytomous logistic regression deals with predicting outcomes that are categorical but not ordered. In many situations, the outcome has some kind of ordering. Using polytomous logistic regression for such situations would lose power to detect the association as well as misinterpret the way the outcome variable is related to the exposure variables.

Ordered factors

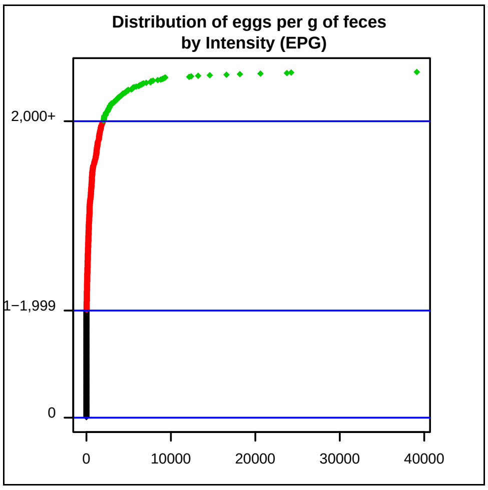
This chapter uses a dataset from a survey on hookworm infections in southern Thailand conducted in 1993. The objective is to document the effect of age and shoe wearing ('shoes') on the intensity of the infection.

```
> library(nnet) # For polytomous logistic regression
> library(MASS) # For ordinal logistic regression
> zap()
> data(HW93)
> use(HW93)
> des()
No. of observations = 637
  Variable      Class           Description
1 id            integer
2 epg           numeric         eggs per g of faeces
3 age           integer
4 shoes         factor          Shoe wearing
5 intense       factor          Intensity (EPG)
6 agegr         factor          Age group

> summ()
  No. of observations = 637
  Var. name Obs.  mean    median  s.d.    min. max.
1 id        637   325.38  325     185.79  1    646
2 epg       637   1141.85 207     2961.82 0    39123
3 age       637   25.94   23      19.47   2    78
4 shoes     637   1.396   1       0.489   1    2
5 intense   637   1.834   2       0.652   1    3
6 agegr     637   1.667   2       0.608   1    3
```

The variable 'intense' is a categorical form of the variable 'epg'.

```
> summ(epg, by=intense)
```

```
For intense = 0
  obs. mean   median  s.d.   min.   max.
  197  0      0       0      0      0

For intense = 1-1,999
  obs. mean   median  s.d.    min.   max.
  349  539    345     512.368 23     1910

For intense = 2,000+
  obs. mean   median  s.d.     min.   max.
  91   5930   3960    5792.453 2020   39100
```



Using polytomous logistic regression

```
> poly.hw <- multinom(intense ~ agegr + shoes)
> mlogit.display(poly.hw)

Outcome =intense; Referent group = 0
               1-1,999
               Coeff./SE      RRR(95%CI)
(Intercept)    0.29/0.138*    -
agegr15-59 yrs 0.87/0.216***  2.39(1.56,3.65)
agegr60+ yrs   0.77/0.41      2.16(0.97,4.82)
shoesyes       -0.48/0.212*   0.62(0.41,0.94)

               2,000+
               Coeff./SE       RRR(95%CI)
(Intercept)    -0.97/0.204***  -
agegr15-59 yrs 1.03/0.306***   2.8(1.54,5.1)
agegr60+ yrs   1.8/0.478***    6.05(2.37,15.44)
shoesyes       -1.34/0.317***  0.26(0.14,0.49)

Residual Deviance: 1196.8
AIC = 1212.8
```

For light infection (1-1,999 epg), only young adults had a higher risk than the children. For heavy infection (2,000+ epg), the young adults and the elder subjects had a 2.8 and 6.1 times higher risk than the children, respectively. Shoe wearing has a protective effect on both light and heavy infection with odds ratios of 0.62 and 0.262, respectively.

Modelling ordinal outcomes

Alternatively, since intensity is an ordered outcome variable, it is worth trying ordinal logistic regression. The command `polr` from the **MASS** package will do this. But first we have to tell **R** that the outcome is ordered.

```
> class(intense)       # "factor"
> intense.ord <- ordered(intense)
> class(intense.ord)   # "ordered" "factor"
> ord.hw <- polr(intense.ord ~ agegr + shoes)
> summary(ord.hw)

Coefficients:
                   Value Std. Error   t value
agegr15-59 yrs  0.7744521  0.1834157  4.222388
agegr60+ yrs    1.2797213  0.3226504  3.966278
shoesyes       -0.7234746  0.1780106 -4.064223

Intercepts:
               Value   Std. Error t value
0|1-1,999      -0.6301  0.1293    -4.8726
1-1,999|2,000+  2.0745  0.1579    13.1363

Residual Deviance: 1204.920
AIC: 1214.920
```

This ordinal logistic regression model has two intercepts, one for each cut point of the outcome. The values of these intercepts are not so meaningful and can be ignored at this stage. The coefficients of all independent variables are shared by two cut points of the dependent variable. At the first cut point, the logit of getting any infection (intense= 1- 1,999 and 2,000 + epg vs no infection) is reduced by 72% if the subject wore shoes, so is the logit at the second cut point (intensity of 2,000 + epg vs any lower levels of intensity). Both coefficients are positive indicating that the risk of infection increases with age. Shoe wearing has a negative coefficient indicating that it protects both levels of infection.

```
> summary(ord.hw) -> s1
> attributes(s1)
```

To compute the P value for 'shoes', type:

```
> coef(s1)
> t <- coef(s1)[,3]
> df <- s1$df.residual
> pt(abs(t), df, lower.tail=F)
agegr15-59 yrs   agegr60+ yrs       shoesyes
  1.386181e-05   4.067838e-05   2.713385e-05
     0|1-1,999 1-1,999|2,000+
  6.969506e-07   2.521906e-35
```

The above commands define 't' and 'df' from the summary of the regression. The last command uses the absolute value of 't' for computation of the two-sided P values. All P values are significant.

'ordinal.or.display'

Epicalc has a function to display ordinal odds ratios and 95% confidence intervals.

```
> ordinal.or.display(ord.hw)
               Ordinal OR lower95ci upper95ci P.value
agegr15-59 yrs 2.169      1.517     3.116     1.39e-05
agegr60+ yrs   3.596      1.913     6.788     4.07e-05
shoesyes       0.485      0.341     0.686     2.71e-05
```

The conclusion from this ordinal logistic regression model is that intensity of infection significantly increases with age group and is significantly reduced by wearing shoes. At each cut point of the intensity of infection, on the average, wearing shoes is associated with a reduction of 0.48 or a half of the odds of those not wearing shoes.

References

Venables, W. N. and Ripley, B. D. (2002) Modern Applied Statistics with S. Fourth edition. Springer.

Exercise

The level of pain after treatment (1 = no pain, 2 = some pain, 3 = severe pain) was measured after treatment of one group of subjects with a pain killer (Drug = 1) against placebo (Drug = 0) in males (1) and females (0) with the following data:

```
Male   0   0   0   0   0   0   1   1   1   1   1   1
Drug   0   1   0   1   0   1   0   1   0   1   0   1
Pain   1   2   3   1   2   3   1   2   3   1   2   3
Total  3   5  15  10   5   7   8   5  10  10  10   2
```

Analyse the effect of this drug with adjustment for sex using polytomous and ordinal logistic regression.

Chapter 19: Poisson and Negative Binomial Regression

The Poisson distribution

In nature, an event usually takes place in a very small amount of time. At any given point of time, the probability of encountering such an event is very small. Instead of probability, measurement is focused on density, which means incidence or 'count' over a period of time. While time is one dimension, the same concept applies to the density of counts of small objects in a two-dimensional area or three-dimensional space.

When one event is independent from another, the occurrence is at random. Mathematically, it can be proved that under this condition, the densities in different units of time vary with a variance equal to the average density. When the probability of having an event is affected by some factors, a model is needed to explain and predict the density. Variation among different strata is explained by the factors. Within each stratum, the distribution is random.

Poisson regression

Poisson regression deals with outcome variables that are counts in nature (whole numbers or integers). Independent covariates are similar to those encountered in linear and logistic regression.

In epidemiology, Poisson regression is used for analysing grouped cohort data, looking at incidence density among person-time contributed by subjects of similar characteristics of interest.

Poisson regression is one of three common generalized linear models (GLM) used in epidemiological studies. The other two that are more commonly used are linear regression and logistic regression, which have been covered in previous chapters.

There are two main assumptions for Poisson regression. Firstly, risk is homogeneous among person-times contributed by different subjects who have the same characteristics of interest (e.g. sex, age-group) and the same period. Secondly, asymptotically, or as the sample size becomes larger and larger, the mean of the counts is equal to the variance.

Benefits of Poisson regression models

Straightforward linear regression methods (assuming constant variance, normal errors) are not appropriate for count data for four main reasons:

1. the model might lead to the prediction of negative counts,

2. the variance of the response may increase with the mean,

3. the errors will not be normally distributed,

4. zero counts are difficult to handle in transformations.

Poisson regression eliminates some of the problems faced by other regression techniques. For example, in logistic regression, different subjects may have different person-times of exposure. Analysing risk factors while ignoring differences in person-times is therefore wrong. In survival analysis using Cox regression (discussed in chapter 22), only the hazard ratio and not incidence density of each subgroup is computed. The analysts and the readers may not have a clear idea on the descriptive statistics of these baseline risks. In other words, Poisson regression produces both 'baseline incidence density' as well as 'incidence density ratio' among strata.

Example: Montana smelter study

The dataset **`Montana`** was extracted from an occupational cohort study conducted to test the association between respiratory deaths and exposure to arsenic in the industry, after adjusting for various other risk factors. The main outcome variable is 'respdeath'. This is the count of the number of deaths among 'personyrs' or person-years of subjects in each category. The other variables are independent covariates including age group 'agegr', period of employment 'period', starting time of employment 'start' and the level of exposure to arsenic during the study period 'arsenic'. Read in the data first and examine the variables.

```
> zap()
> data(Montana)
> use(Montana)
> summ()

No. of observations = 114

  Var. name Obs.  mean    median  s.d.   min.  max.
1 respdeath 114   2.42    1       3.3    0     19
2 personyrs 114   1096.41 335.15  2123.1 4.2   12451
3 agegr     114   2.61    3       1.1    1     4
4 period    114   2.4     2       1.09   1     4
5 start     114   1.46    1       0.5    1     2
6 arsenic   114   2.47    2       1.11   1     4
```

```
> des()
No. of observations = 114

  Variable      Class           Description
1 respdeath     integer
2 personyrs     numeric
3 agegr         integer
4 period        integer
5 start         integer
6 arsenic       integer
```

The last four variables are classed as integers. We need to tell **R** to interpret them as categorical variables, or factors, and attach labels to each of the levels. This can be done using the `factor` command with a 'labels' argument included.

```
> agegr <- factor(agegr, labels=c("40-49","50-59","60-69","70-
  79"))
> period <- factor(period, labels=c("1938-1949", "1950-1959",
  "1960-1969", "1970-1977"))
> start <- factor(start, labels=c("pre-1925", "1925 & after"))
> arsenic1 <- factor(arsenic, labels=c("<1 year", "1-4
  years","5-14 years", "15+ years"))

> label.var(agegr, "Age group")
> label.var(period, "Period of employment")
> label.var(start, "Era of starting employment")
> label.var(arsenic1, "Amount of exposure to arsenic")
> des()

No. of observations =114
  Variable      Class           Description
1 respdeath     integer
2 personyrs     numeric
3 agegr         factor          Age group
4 period        factor          Period of employment
5 start         factor          Era of starting employment
6 arsenic       integer
7 arsenic1      factor          Amount of exposure to arsenic
```

We keep the original 'arsenic' variable unchanged for use later on.

Breakdown of incidence by age and period

Let us explore the person-years breakdown by age and period. Firstly, create a table for total person-years:

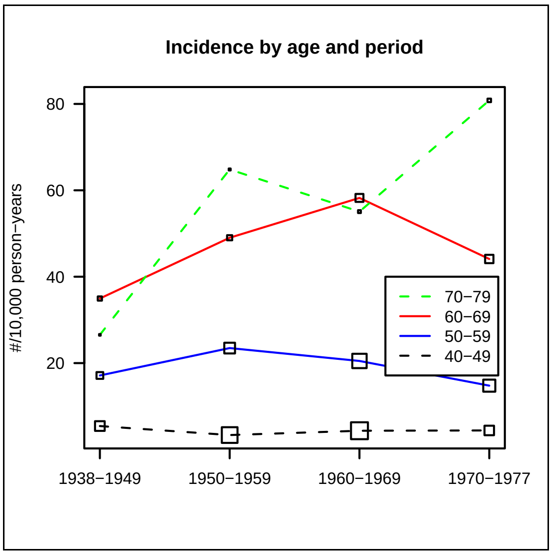
```
> tapply(personyrs, list(period, agegr), sum) -> table.pyears
```

Carry out the same procedure for number of deaths, and compute the table of incidence per 10,000 person years for each cell.

```
> tapply(respdeath, list(period, agegr), sum) -> table.deaths
> table.inc10000 <- table.deaths/table.pyears*10000
> table.inc10000
             40-49    50-59    60-69    70-79
1938-1949 5.424700 17.13102 34.95107 26.53928
1950-1959 3.344638 23.47556 49.01961 64.82632
1960-1969 4.341516 20.49375 58.23803 55.06608
1970-1977 4.408685 14.77747 44.09949 80.81413
```

Now, create a time-series plot of the incidence:

```
> plot.ts(table.inc10000, plot.type="single", xlab=" ",
   ylab="#/10,000 person-years", xaxt="n", col=c("black",
   "blue","red","green"), lty=c(2,1,1,2), las=1)

> points(rep(1:4,4), table.inc10000, pch=22, cex=table.pyears
   / sum(table.pyears) * 20)

> title(main = "Incidence by age and period")

> axis(side = 1, at = 1:4, labels = levels(period))

> legend(3.2,40, legend=levels(agegr)[4:1], col=c("green",
   "red", "blue", "black"), bg = "white", lty=c(2, 1, 1, 2))
```



The above graph shows that the older age group is generally associated with a higher risk. On the other hand, the sample size (reflected by the size of the squares at each point) decreases with age.

The possibility of a confounding effect of age can better be examined by using Poisson regression.

Modelling with Poisson regression

```
> mode11 <- glm(respdeath ~ period, offset = log(personyrs),
    family = poisson)
> summary(mode11)
==============================
Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept)      -6.4331     0.1715 -37.511   <2e-16
period1950-1959   0.2365     0.2117   1.117   0.2638
period1960-1969   0.3781     0.2001   1.889   0.0588
period1970-1977   0.4830     0.2036   2.372   0.0177

AIC: 596
==============================
```

The option 'offset = log(personyrs)' allows the variable 'personyrs' to be the denominator for the counts of 'respdeath'. A logarithmic transformation is needed since, for a Poisson generalized linear model, the link function is the natural log, and the default link for the Poisson family is the log link.

An important criterion in the choice of a link function for various families of distributions is to ensure that the fitted values from the modelling stay within reasonable bounds. Specifying a log link (default for Poisson) ensures that the fitted counts are all greater than or equal to zero.

Note:

For more details on default links for various families of distributions related to generalized linear modelling, see the help in **R** under 'help(family)'.

The first model above of Poisson regression with 'period' as the only independent variable suggests that the death rate increased with time. The model can be tested for goodness of fit and the checked whether the Poisson assumptions mentioned earlier in the chapter have been violated.

Goodness of fit test

To test the goodness of fit of the Poisson model, type:

```
> poisgof(mode11)
$results
[1] "Goodness-of-fit test for Poisson assumption"

  $chisq
[1] 369.27

  $df
[1] 110

  $p.value
[1] 9.5784e-30
```

The component '$chisq' is actually computed from the model deviance, a parameter reflecting the level of errors. A large chi-squared value with small degrees of freedom results in a significant violation of the Poisson assumption ($p < 0.05$). If only the P value is wanted, the command can be shortened.

```
> poisgof(mode11)$p.value
```

The P value is very small indicating a poor fit.

Note: ____

It should be noted that this method is under assumption of a large sample size. An alternative method is to a fit negative binomial regression model and check if the parameters are different from 1, which is demonstrated in the latter section of this chapter.

We now add the second independent variable 'agegr' to the model.

```
> mode12 <- glm(respdeath~agegr+period, offset=log(personyrs),
   family = poisson)
> AIC(mode12)  # 396.64
```

The AIC has decreased remarkably from '`model1`' to '`model2`' indicating a poor fit of the first model.

```
> poisgof(mode12)$p.value   # 0.00032951
```

However the second model, '`model2`', still violates the Poisson assumption.

```
> mode13 <- glm(respdeath ~ agegr, offset = log(personyrs),
   family = poisson)
> AIC(mode13) # 394.47
> poisgof(mode13)$p.value   # 0.0003295
```

Removal of 'period' further reduces the AIC but still violates the Poisson assumption to the same extent as the previous model. The next step is to add the main independent variable 'arsenic1'.

```
> mode14 <- glm(respdeath ~ agegr+arsenic1, offset=log(personyrs),
  family = poisson)
> summary(mode14)
Coefficients:
                   Estimate Std. Error z value Pr(>|z|)
(Intercept)          -7.995      0.224  -35.74  < 2e-16
agegr50-59            1.462      0.245    5.96  2.5e-09
agegr60-69            2.350      0.238    9.87  < 2e-16
agegr70-79            2.599      0.256   10.14  < 2e-16
arsenic11-4 years     0.804      0.158    5.10  3.4e-07
arsenic15-14 years    0.596      0.206    2.89   0.0038
arsenic115+ years     0.998      0.176    5.67  1.4e-08

    Null deviance: 376.02  on 113  degrees of freedom
Residual deviance: 122.25  on 107  degrees of freedom
AIC: 355.0

> poisgof(mode14)$p.value   # 0.14869
```

The last model, '`model4`', has a much lower AIC than '`model3`' and it now does not violate the assumption. One or more years of arsenic exposure is associated with a higher incidence of respiratory deaths.

Linear dose response relationship

Alternatively, instead of including arsenic as a categorical variable, it can be included in the model as a continuous variable. If the P vaue is significant then this would imply that there is a linear dose-response relationship between exposure to arsenic and the risk for the disease. The original variable 'arsenic' is included in the next model.

```
> model5 <- glm(respdeath~agegr+arsenic, offset=log(personyrs),
    family=poisson)
> summary(model5)
=============================
Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)  -8.2416     0.2327  -35.42  < 2e-16
agegr50-59    1.4572     0.2454    5.94  2.9e-09
agegr60-69    2.3236     0.2379    9.77  < 2e-16
agegr70-79    2.5572     0.2558   10.00  < 2e-16
arsenic       0.3358     0.0524    6.40  1.5e-10
AIC: 360.31

> poisgof(model5)$p.value   # 0.069942
```

Although the linear term is significant, the AIC value in '`model5`' is higher than that of '`model4`'. It would therefore be better keeping arsenic as factor. However, from '`model4`' there does not appear to be any increase in the risk of death from more than 4 years of exposure to arsenic so it may be worth combining it into just two levels.

```
> arsenic2 <- arsenic1
> levels(arsenic2) <- c("<1 year", rep("1+ years", 3))
> label.var(arsenic2, "Exposure to arsenic")
> model6 <- glm(respdeath ~ agegr + arsenic2,
  offset=log(personyrs), family=poisson)
> summary(model6)
============================
Coefficients:
                 Estimate Std. Error z value Pr(>|z|)
(Intercept)        -8.009      0.223  -35.86  < 2e-16
agegr50-59          1.470      0.245    5.99  2.0e-09
agegr60-69          2.366      0.237    9.98  < 2e-16
agegr70-79          2.624      0.255   10.30  < 2e-16
arsenic21+ years    0.811      0.121    6.70  2.1e-11
============================
AIC: 353.8

> poisgof(model6)$p.value   # 0.13999
```

At this stage, we would accept '`model6`' as the model of choice as it has the smallest AIC among all the models that we have tried. We conclude that exposure to arsenic for at least one year would increase the risk for the disease by exp(0.8109) or 2.25 times with statistical significance.

Incidence density

In the Poisson model, the outcome is a *count*. In the general linear model, the relationship between the values of the outcome (as measured in the data and predicted by the model in the fitted values) and the linear predictor is determined by the link function. This link function relates the mean value of the outcome to its linear predictor. By default, the link function for the Poisson distribution is the natural logarithm. With the offset being log(person-time), the value of the outcome becomes log(incidence density).

The matrix 'table.inc10000' (created previously) gives the crude incidence density by age group and period. Each of the Poisson regression models above can be used to compute the predicted incidence density when the variables in the model are given. For example, to compute the incidence density from a population of 100,000 people aged between 40-49 years who were exposed to arsenic for less than one year using '`model6`', type:

```
> newdata <- as.data.frame(list(agegr="40-49",
   arsenic2="<1 year", personyrs=100000))
> predict(model6, newdata, type="response")
[1] 33.257
```

This population would have an estimated incidence density of 33.26 per 100,000 person-years.

Incidence density ratio

In a case control study, the odds ratio is used to compare the prevalence of exposure among cases and controls. In a cohort study, this value is equal to the ratio between the odds of getting a disease among the exposed and the unexposed group. If the disease is rare, the odds is close to the probability or risk. The ratio of the risks for the two groups is then called the 'risk ratio' or the 'relative risk'.

In a real cohort study, subjects do not always have the same follow-up duration. The relative risk ignores the duration of follow up. Therefore it is not a good measure of comparison of risk between the two groups. In this chapter, all subjects pool their follow-up times and this number is called 'person time', which is then used as the denominator for the event, resulting in 'incidence density'. Comparing the incidence density among two groups of subjects by their exposure status is fairer than comparing the crude risks. The ratio between the incidence densities of two groups is called the incidence density ratio (IDR), which is an improved form of'relative risk.

In '`model6`', to compute the incidence density ratio between the subjects exposed to arsenic for one or more years against those exposed for less than one year, we can divide the incidence among the former by that among the latter group.

```
> levels(newdata$arsenic2) <- c("<1 year", "1+ years")
> newdata <- rbind(newdata, list(agegr="40-49",
    arsenic2="1+ years", personyrs=100000))
> newdata
  agegr arsenic2 personyrs
1 40-49  <1 year     1e+05
2 40-49 1+ years     1e+05
> id <- predict(model6, newdata, type="response")
> idr.arsenic <- id[2]/id[1]
> idr.arsenic
[1] 2.2499
```

The above procedure starts by appending a new row to the data frame '`newdata`' having everything the same as the first row except that the variable 'arsenic2' is "1+ years". The responses or incidence densities of the two conditions are then computed. The IDR is then obtained from division of the incidence densities for arsenic2="<1 year" with arsenic2="1+ years".

A shorter way to obtain this IDR is to exponentiate the coefficient of the specific variable 'arsenic', which is the fifth coefficient in the model.

```
> coef(model6)
  (Intercept)  agegr50-59  agegr60-69  agegr70-79 arsenic21+
     -8.00865     1.47015     2.36611     2.62375    0.81087

> exp(coef(model6)[5])
arsenic21+ years
          2.2499
```

'idr.display' to get 95% CI of IDR

The following steps explain how the 95% confidence interval of IDR for all variables can be obtained.

```
> coeff <- coef(model6)
> coeff.95ci <- cbind(coeff, confint(model6))
```

Note that `confint(glm6)` provides a 95% confidence interval for the model coefficients.

```
> IDR.95ci <- round(exp(coeff.95ci), 1)[-1,]
```

The required values are obtained from exponentiating the last matrix with the first row or intercept removed. The display is rounded to 1 decimal place for better viewing. Then the matrix column is labelled and the 95% CI is displayed.

```
> colnames(IDR.95ci) <- c("IDR", "lower95ci", "upper95ci")
> IDR.95ci
```

A simpler way is to use the command *`idr.display`* in *Epicalc*.

```
> idr.display(model6, decimal=1)

Poisson regression predicting respdeath with offset = 
  log(personyrs) 

             crude IDR(95%CI)  adj. IDR(95%CI)  P(Wald's)  P(LR-test)
agegr: ref.=40-49                                          < 0.001
   50-59      4.5 (2.8,7.3)    4.3 (2.7,7)      < 0.001
   60-69     11.3 (7.1,17.9)  10.7 (6.7,17)     < 0.001
   70-79     14.5 (8.8,23.8)  13.8 (8.4,22.7)   < 0.001

arsenic2      2.5 (2,3.1)     2.2 (1.8,2.9)     < 0.001     < 0.001
   1+ years vs <1 year

Log-likelihood =  -171.9
No. of observations =  114
AIC value = 353.8
```

The command *idr.display* gives results to 3 decimal places by default. This can easily be changed by the user.

Negative binomial regression

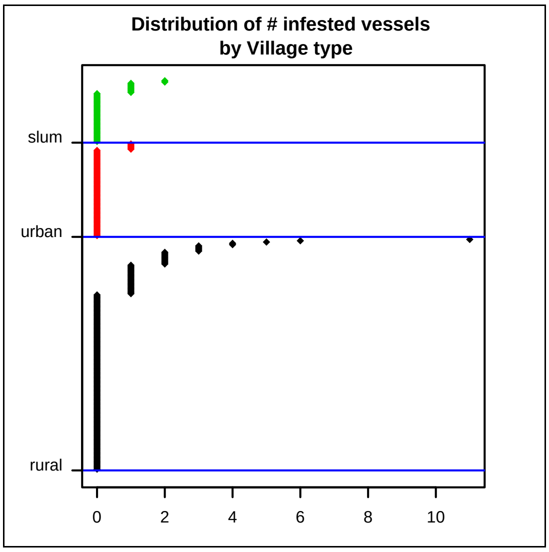
Recall that for Poisson regression, one of the assumptions for a valid model is that the mean and variance of the count variable are equal. The negative binomial distribution is a more generalized form of distribution used for count response data, allowing for greater dispersion or variance of counts. In practice, it is quite common for the variance of the outcome to be larger than the mean. This is called overdispersion. If a count variable is overdispersed, Poisson regression underestimates the standard errors of the predictor variables. When overdispersion is evident, one solution is to specify that the errors have a negative binomial distribution.

Negative binomial regression gives the same coefficients as those from Poisson regression but give larger standard errors. The interpretation of the results is the same as that from Poisson regression.

Take an example of counts of water containers infested with mosquito larvae in a field survey. The data is contained in the dataset **DHF99**.

```
> library(MASS)
> data(DHF99); use(DHF99)
> des()
No. of observations = 300
  Variable      Class           Description
1 houseid       integer         no
2 village       integer         Village
3 education     factor          Educational level
4 containers    integer         # infested vessels
5 viltype       factor          Village type
```

```
> summ()

No. of observations = 300

  Var. name  obs. mean   median  s.d.   min.   max.
1 houseid    300  174.27 154.5   112.44 1      385
2 village    300  48.56  51      32.25  1      105
3 education  300  2.09   1       1.455  1      5
4 containers 299  0.35   0       1.01   0      11
5 viltype    300  1.56   1       0.754  1      3

> summ(containers, by=viltype)

For viltype = rural
  obs. mean   median  s.d.   min.   max.
  179  0.492  0       1.251  0      11

For viltype = urban
  obs. mean   median  s.d.   min.   max.
  72   0.069  0       0.256  0      1

For viltype = slum
  obs. mean   median  s.d.   min.   max.
  48   0.25   0       0.526  0      2
```



The function for performing a negative binomial glm is `glm.nb`. This function is located in the **MASS** library. In addition, a very helpful function for selecting the best model based on the AIC value is the `step` function, which is located in the **stats** library (a default library loaded on start-up).

```
> model.poisson <- step(glm(containers ~ education + viltype,
  family=poisson, data=.data))
```

```
> model.nb <- step(glm.nb(containers ~ education + viltype,
  data=.data))

> coef(model.poisson)
 (Intercept) viltypeurban  viltypeslum 
  -0.7100490   -1.9571792   -0.6762454 

> coef(model.nb)
 (Intercept) viltypeurban  viltypeslum 
  -0.7100490   -1.9571792   -0.6762454 
```

Both models end up with only 'viltype' being selected. The coefficients are very similar. The Poisson model has significant overdispersion but not the negative binomial model.

```
> poisgof(model.poisson)$p.value
[1] 0.0043878

> poisgof(model.nb)$p.value
[1] 1
```

The AIC of the negative binomial model is also better (smaller) than that of the Poisson model.

```
> model.poisson$aic
[1] 505.92

> model.nb$aic
[1] 426.23
```

Finally, the main differences to be examined are the standard errors of the coefficients, the 95% confidence intervals and P values.

```
> summary(model.poisson)$coefficients
               Estimate Std. Error   z value     Pr(>|z|)
(Intercept)  -0.7100490  0.1066000 -6.660873 2.722059e-11
viltypeurban -1.9571792  0.4597429 -4.257117 2.070800e-05
viltypeslum  -0.6762454  0.3077286 -2.197538 2.798202e-02

> summary(model.nb)$coefficients
               Estimate Std. Error   z value     Pr(>|z|)
(Intercept)  -0.7100490  0.1731160 -4.101578 4.103414e-05
viltypeurban -1.9571792  0.5255707 -3.723912 1.961591e-04
viltypeslum  -0.6762454  0.4274174 -1.582166 1.136116e-01

> idr.display(model.poisson)
               IDR lower95ci upper95ci P value
viltypeurban 0.141     0.057     0.348   0.000
viltypeslum  0.509     0.278     0.930   0.028

> idr.display(model.nb)
               IDR lower95ci upper95ci P value
viltypeurban 0.141      0.05     0.396   0.000
viltypeslum  0.509      0.22     1.175   0.114
```

The standard errors from the negative binomial model are slightly larger than those from the Poisson model resulting in wider 95% confidence intervals and larger P values. From the Poisson regression, both urban community and slum area had a significantly lower risk (around 14% and a half reduction, respectively) for infestation. However, from the negative binomial regression, only the urban community had a significantly lower risk.

References

Agresti, A. (1996). An Introduction to Categorical Data Analysis. New York: John Wiley and Sons.

Agresti, A. (2002). Categorical Data Analysis. Hoboken, NJ: John Wiley and Sons.

Powers, D.A., Xie, Y. (2000). Statistical Methods for Categorical Data Analysis. San Diego: Academic Press.

Long, J.S. (1997). Regression Models for Categorical and Limited Dependent Variables. Thousand Oakes, CA: Sage Publications.

Vermunt, J.K. (1997). Log-linear Models for Event Histories. Thousand Oakes, CA: Sage Publications.

Exercise

Use `step` to select the best model predicting incidence densities of the **`Montana`** dataset. Check the Poisson goodness of fit. Compute the incidence density ratio for significant independent variables. Fit a negative binomial regression model to check the theta (dispersion parameter) and its standard error term before concluding whether there is any evidence of overdispersion.

Chapter 20: Introduction to Multi-level Modelling

There are many other names for multi-level modelling, e.g. hierarchical modelling, mixed effects modelling, modelling with random effects. They are all the same. Each name has its own implication.

In epidemiological studies, variables often have a hierarchy. For example, measurement of blood pressure belongs to an individual subject who can have more than one measurement. In this case, the individual person is at higher hierarchy than each measurement. An individual, however, belongs to a family, all members of which may share several independent variables, such as ethnicity, housing, etc. In turn a family is usually a member of a village, and so forth. Thus the hierarchy can be country, province, district, village, family, individual and measurement. Certain independent variables will be at the individual measurement level, such as time of measurement. Some variables may belong to a higher hierarchical order, such as sex and age (individual), ethnicity (family), and distance from the capital city (village). Independent variables at different levels of the hierarchy should not be treated in the same way. For this reason multi-level modelling is also called hierarchical modelling.

In another aspect, modelling is usually meant for explanation of the relationship of variables in an informative and efficient manner. In simple modelling, where the number of groups are not high, say *m* ethnic groups under study, the number of parameters used to explain the effect of 'ethnic' is *m*-1 because the omitted one is used as the referent group. If the sample size is large and *m* is small the number of parameters used would not be too high. On the other hand, if the sample size is small but the number of groups is high, for example, 50 subjects with multiple blood pressure measurements, the grouping variables would have too many levels too put into the model. To do this, an average value for the group is computed and the individual members are treated as random effects without a parameter. In this situation, multi-level modelling is also called modelling with random effects. However, the random effects must always have an average, which is used to estimate the overall effect. This average or overall effect is called the fixed effects. With the mixture of fixed and random effects in the same model, multi-level modelling is also called 'mixed effects modelling'.

Multi-level modelling is relatively new compared to other common types of modeling, such as linear and Poisson regression. There are variations in the methods of numerical iteration for computation of coefficients and standard errors. They generally give very close estimates but different standard errors, variances and covariances. The examples in this chapter are confined to the 'glmmPQL' function or Generalized Linear Mixed Models using Penalized Quasi-Likelihood. It can handle all families used in GLMs with similar arguments in the command except the additional terms defining the fixed and random effects. Readers are advised to explore other functions such as `lme` (linear mixed effects) and `nlme` (non-linear mixed effects).

From stratified analysis to random effects modelling

Analysis of the effect of putting additional table salt into the meal in chapter 12 was carried out having two strata, each with a relatively high number of subjects. The stratification factor (salt adding) has two levels 'yes/no' but only one parameter in the model.

In a setting with a high number of strata, each with a relatively small number of records, including individual strata would add too many parameters to the model, thus reducing the efficiency of explanation (too many variables used for explaining a small dataset). To solve this problem, each stratum is represented by the strata mean and each sample stratum is taken as a random member of the sets of strata in the population. Therefore, regardless of how large the number of strata is, there would be only two parameters from the stratification factor: the mean and variance (or standard deviation).

Example: Orthodontic Measurements

An example for such a situation, and the commands for computation, are available from the **nlme** library. The growth of 27 children (16 boys and 11 girls) was assessed by measuring the distance from the pituitary to pterygomaxillary fissure. Measurements were made on each child every 4 years (ages 8, 10, 12 and 14 years).

The data is in hierarchical order. A child has more than one measurement recorded over time. The individual records or measurements are at level 1 whereas the individual children are at level 2. Age is also in level 1 since it can vary within individual subjects, although the variation is constant for all children. On the other hand, sex is at level 2, which is fixed for each child.

Each child can be initially interpreted as a stratum. The 27 strata are taken as a random sample of infinite population of strata.

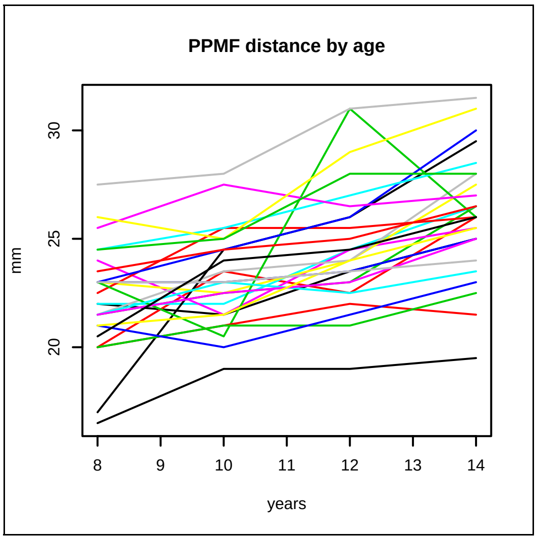
For the simplest multi-level modelling, the coefficient of 'age', or the slope of the regression lines, is estimated as a single parameter, i.e. all subjects are assumed to have the same growth rate. For the intercept, the model estimates the population 'mean intercept' and population standard deviation of the intercepts. The intercept has 'random effects' (for individual children) whereas the slope has a 'fixed effect' for the whole group. Combining these two types of random and fixed effects, the model is often called a 'mixed model'.

Once the library **nlme** has been loaded, the dataset **`Orthodont`** can be used. Be careful as some of the variable names in this data frame start with upper case.

```
> zap()
> library(MASS) # For the glmmPQL command
> library(nlme) # For the example dataset
> data(Orthodont)
> .data <- as.data.frame(Orthodont)
> use(.data);  des()

No. of observations =108
  Variable      Class           Description
1 distance      numeric         distance
2 age           numeric         age
3 Subject       factor          Subject
4 Sex           factor          Sex

> summ()
  Var. name Obs.   mean   median  s.d.   min.   max.
1 distance  108    24.02  23.75   2.93   16.5   31.5
2 age       108    11     11      2.25   8      14
3 Subject   108    14     14      7.825  1      27
4 Sex       108    1.407  1       0.494  1      2
```

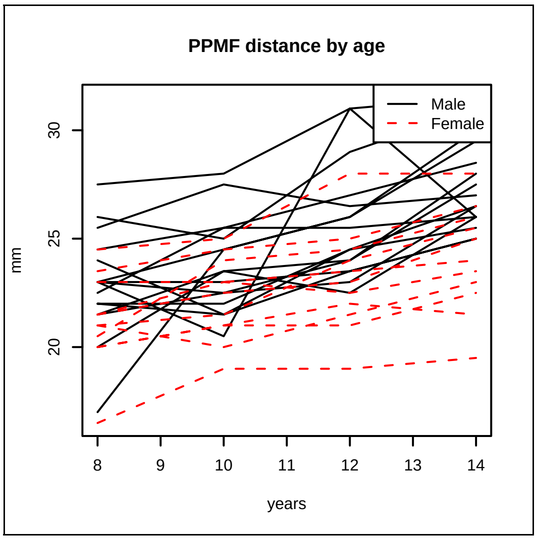
A follow-up plot is useful to visualize the data. *Epicalc* has a function called *`followup.plot`*, which plots the outcome for each subject over time.

```
> followup.plot(id=Subject, time=age, outcome=distance,
    line.col="multicolor")
> title(main="PPMF distance by age", ylab="mm", xlab="years")
```



To see whether there is a gender difference, we replace the 'lines' argument with the 'by' argument in the command.

```
> followup.plot(id=Subject,time=age,outcome=distance,by=Sex)
> title(main="PPMF distance by age", ylab="mm", xlab="years")
```



In both plots, it is evident that as age increases so does distance. The rates of individuals are however criss-crossing to a certain extent. Otherwise, the highest and the lowest lines are quite consistent. Males generally had larger pituitary to pterygomaxillary fissure distances.

Random intercepts model

For multi-level modelling, each subject is taken as a stratum. For this first model, the slopes are forced to be the same. There are 27 intercepts; too many to have each of them as a parameter. Instead, a mean intercept is computed and the remaining are taken as random effects.

```
> model0 <- glmmPQL(distance ~ age, random = ~1 | Subject,
    data = .data, family = gaussian)
```

The above command creates a generalized linear multi-level model (glmm) using the Penalized Quasi-Likelihood (PQL) method of iteration. The dependent variable is 'distance'. The independent variable is 'age', which has fixed effects (for all subjects). The random effects (as indicated by the word 'random') is a constant of 1. The upper level of the model (following the '|' sign) is 'Subject' because the same subject has 4 repeated measurements. In other words, 'Subject' is at a higher level. The `glmmPQL` command handles the 'family' argument of the model in the same way as the `glm` command. Since the errors are assumed to be normally distributed, the family is specified as 'gaussian'.

```
> summary(model0)
Linear mixed-effects model fit by maximum likelihood
 Data: .data
  AIC BIC logLik
   NA  NA     NA

Random effects:
 Formula: ~1 | Subject
        (Intercept) Residual
StdDev:    2.072142 1.422728

Variance function:
 Structure: fixed weights
 Formula: ~invwt
Fixed effects: distance ~ age
                Value Std.Error DF  t-value p-value
(Intercept) 16.761111 0.8020244 80 20.89851       0
age          0.660185 0.0617993 80 10.68272       0
 Correlation:
    (Intr)
age -0.848

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-3.68695131 -0.53862941 -0.01232442  0.49100161  3.74701484

Number of Observations: 108
Number of Groups: 27
```

The 'AIC' and 'BIC' values are derived from 'logLik', the log likelihood. They will be used to compare the level of fit with other models using the same dataset and the same method of iteration. Note that AIC is equal to -2×logLik + 2×*npar* and BIC is equal to -2×logLik + log(*n*)×*npar*, where *npar* is the number of parameters in the model (in this model, four; namely, the standard deviations of intercepts and residuals, which are the random effects, and the coefficient of the fixed intercept and the fixed effect of age) and *n* is the number of observations (108).

Random effects express themselves as standard deviations of errors. There are two parts of errors. The first part is the standard deviations of difference between the fixed intercept and the intercepts of individual subjects. The second part is the standard deviation of the residuals or the difference between the final predicted values and the observed values for each subject. There is no coefficient for these random effects terms because the means should be close to zero. This is because they are assumed to come from the standard normal distribution.

The fixed part of the summary, similar to a conventional regression model, contains the coefficients and their standard errors. The coefficient of the intercept is 16.76. This means that on the average, at the age of 0, the PPMF distance for a child is expected to be 16.76 mm. The coefficient of age is 0.66. This means that for each birthday reached, an average child is expected to gain 0.66 mm length of PPMF distance. This coefficient is statistically significant as the standard error is relatively small, resulting in a large t-value and a small P value. The standardised residuals within groups (or within the child) are distributed with a certain degree of symmetry since the median is close to 0, and the lower and upper quartiles are relatively equidistant from the median, as are the minimum and the maximum. Finally, the model confirms that there were 27 children giving 108 records.

Model attributes and graphing

The model has many attributes inside. We will examine only some of these.

```
> attributes(model0)
$names
 [1] "modelStruct"  "dims"     "contrasts"    "coefficients"
 [5] "varFix"       "sigma"    "apVar"        "logLik"
 [9] "numIter"      "groups"   "call"         "terms"
[13] "method"       "fitted"   "residuals"    "fixDF"
[17] "na.action"    "data"     "family"

$class
[1] "glmmPQL" "lme"
```

The most important attributes are the coefficients.

```
> coef(model0)
$fixed
(Intercept)         age
 16.7611111   0.6601852
$random
$random$Subject
    (Intercept)
M16  -0.9152788
M05  -0.9152788
M02  -0.5798146
===============
===============
F04   0.7620421
F11   2.1038989
```

There are two parts of the coefficients: the fixed part and the random part. The fixed part, shown in the summary, is the average for all of the 27 strata (children). The fixed intercept is 16.761111, which means that the (average) estimated distance at birth (when age is 0) is 16.76 mm. For each increasing year of age, the PPMF distance increases by approximately two-thirds of a millimetre (0.66). The second or random part shows 'random intercepts only' since there is no variable in this part as specified by 'random ~ 1'. There are 27 (additional coefficients for) intercepts, one for each child. For the first child (M16) who has a negative random intercept, or starting distance, the mean intercept from the fixed part (16.76) must be subtracted by 0.9152788. The second person (M05) shares the same intercept. Altogether, the random intercepts range from -4.940849 (F10) to +4.899434 (M10).

There are many other attributes worth exploring. The next interesting one is 'fitted(model0)', which contains the fitted or predicted values of each point of observation.

```
> model0$fitted
     fixed Subject
1   22.043  25.377
2   23.363  26.697
3   24.683  28.017
4   26.004  29.338
5   22.043  21.463
6   23.363  22.783
7   24.683  24.104
8   26.004  25.424
==== Up to 108th person ==========
```

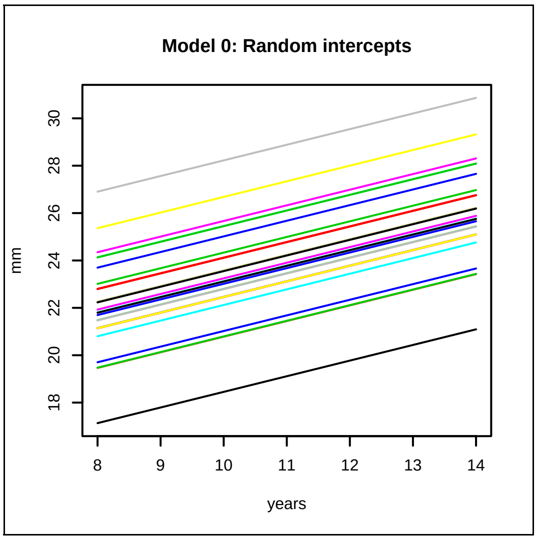
There are two columns of fitted values: fixed (average of each point of time) and random (by Subject). In fact, the fixed part has only four values predicting the average value for each value of age.

```
> tab1(model0$fitted[, 1])
[model0$fitted  1 :
                  Frequency Percent
22.0425925925926        27      25
23.3629629629630        27      25
24.6833333333333        27      25
26.0037037037037        27      25
  Total                108     100
```

Each value has 27 repeated records. In other words, there are only four terms of fixed effects, each shared by all 27 subjects. The second component is predicting the intercept value for each subject, which varies from one child to another.

```
> followup.plot(id=Subject, time=age, outcome=fitted(model0),
    line.col="multicolor")

> title(main="Model 0: random intercepts", ylab="mm",
    xlab="years")
```

The X-coordinates for each line are the ages for that child. The corresponding Y-coordinates are the fitted values for the PPMF distance. Recall that there are two columns for the fitted values (for the fixed and random effects). The plot uses the second column, which is the predicted value for each child (random effects). The colour varies according to the (order of) 'Subject'.



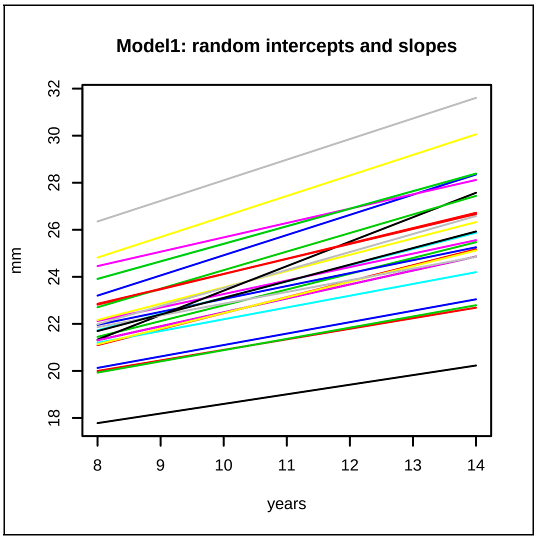
The model fixes the coefficient of the slope, allowing only the intercepts to be a random variable. The next model releases the effects of age to become random with a mean value.

Model with random slopes

```
> model1 <- glmmPQL(distance ~ age, random = ~age | Subject,
    data = .data, family = gaussian)

> summary(model1)
Linear mixed-effects model fit by maximum likelihood
 Data: .data
   AIC BIC logLik
    NA  NA     NA

Random effects:
 Formula: ~age | Subject
 Structure: General positive-definite, Log-Cholesky
  parametrization
            StdDev    Corr
(Intercept) 2.2023778 (Intr)
age         0.2152392 -0.585
Residual    1.3103646
Variance function:
 Structure: fixed weights
 Formula: ~invwt
Fixed effects: distance ~ age
                Value Std.Error DF   t-value p-value
(Intercept) 16.761111 0.7689227 80 21.798174       0
age          0.660185 0.0706254 80  9.347699       0
 Correlation:
    (Intr)
age -0.849

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-3.30002923 -0.48692999  0.00739127  0.48148182  3.92211226

Number of Observations: 108
Number of Groups: 27
```

Similar to `'model0'`, a graph can be plotted with the following commands.

```
> followup.plot(id=Subject, time=age, outcome=fitted(glmm1),
    line.col="multicolor")

> title(main="Model1: random intercepts and slopes",
    ylab="mm", xlab="years")
```



Model `'model0'` is equivalent to a stratified analysis without interaction whereas `'model1'` is equivalent to keeping an interaction term. The latter model suggests that each child has their own baseline distance (intercept) as well as their own growth rate.

The graph shows different slopes for different subjects. The slopes are now a random effect as well as a fixed effect.

In the random effects part, age has a standard deviation of 0.215 mm, which is relatively small compared to the randomness of the intercept (2.2 mm) and the residuals (1.3 mm). The variation due to differences in growth rate of the PPMF distance among subjects is small compared to the variation in baselines and the average growth rate. The correlation between age and intercept is negative (-0.585) in the random effects suggesting that the slope of the subjects tends to be flatter as the level of the Y-intercepts increases.

The coefficients of the fixed effects for the intercept and age are not different from `'model0'`. In fact the coefficients are the same as those from ordinary glm.

```
> summary(glm(distance ~ age, family=gaussian))
```

The standard errors from the generalised linear model are much higher than those of the multi-level models. These advanced models improve the precision of the estimates. In this example `'model1'` has wider standard errors than `'model0'`. When the age effect is partially individualised, the overall age effect reduces its precision.

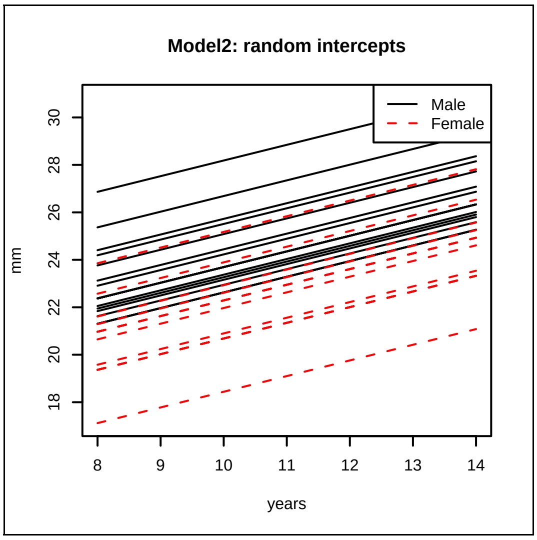
We have another independent variable 'Sex'. It would be interesting to examine whether the boys have larger distance than girls and whether the growth rates are different between the sexes.

```
> model2 <- glmmPQL(distance ~ age + Sex, random = ~1 |
    Subject, data = .data, family = gaussian)

> summary(model2)
Linear mixed-effects model fit by maximum likelihood
 Data: .data
  AIC BIC logLik
   NA  NA     NA

Random effects:
 Formula: ~1 | Subject
        (Intercept) Residual
StdDev:    1.730079 1.422728

Variance function:
 Structure: fixed weights
 Formula: ~invwt
Fixed effects: distance ~ age + Sex
                Value Std.Error DF   t-value p-value
(Intercept) 17.706713 0.8315459 80 21.293729  0.0000
age          0.660185 0.0620929 80 10.632212  0.0000
SexFemale   -2.321023 0.7430668 25 -3.123572  0.0045
========= Remaining parts of output omitted ========
```

'Sex' is introduced as a pure fixed effect. In fact, it cannot be a random effect because there is no variation of sex in an individual subject.

The growth lines are now separated by 'Sex'.

```
> followup.plot(id=Subject, time=age, outcome=fitted(model2),
    by=Sex)

> title(main="Model2: random intercepts", ylab="mm", xlab="years")
```



It is clear that the lines for males tend to be in the upper half of the plot whereas those for females tend to be in the lower part.

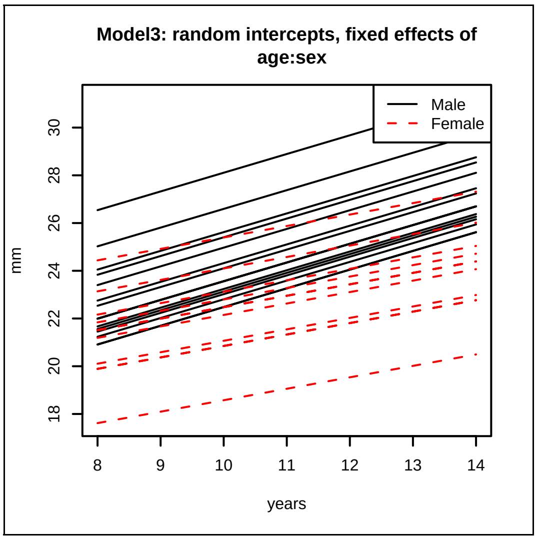
To test whether the rates are different between the two sexes, an interaction term between age and sex is introduced.

```
> model3 <- glmmPQL(distance ~ age*Sex, random = ~1 | Subject,
  data = .data, family = gaussian)
> summary(model3)
Linear mixed-effects model fit by maximum likelihood
 Data: .data
  AIC BIC logLik
   NA  NA     NA

Random effects:
 Formula: ~1 | Subject
        (Intercept) Residual
StdDev:    1.740851 1.369159

Variance function:
 Structure: fixed weights
 Formula: ~invwt
Fixed effects: distance ~ age * Sex
                  Value Std.Error DF   t-value p-value
(Intercept)   16.340625 0.9814310 79 16.649795  0.0000
age            0.784375 0.0779963 79 10.056564  0.0000
SexFemale      1.032102 1.5376069 25  0.671239  0.5082
age:SexFemale -0.304830 0.1221968 79 -2.494580  0.0147
========= Remaining parts of output omitted ========
```

The interaction term between age and sex is significant. The coefficient of the main effect of 'Female' is 1.03, indicating that under a linear growth assumption, at birth (where age is 0), girls have a longer average PPMF distance of 1.03mm compared to boys.

The coefficient of the interaction term is -0.30483 indicating that for each increment of one year, girls will have a shorter average PPMF distance of 0.3mm compared to boys. In other words, females have a shorter PPMF distance and a smaller growth rate.

```
> followup.plot(id=Subject, time=age, outcome=fitted(model3),
    by=Sex)

> title(main="Model3: random intercepts, fixed effects of
    age:sex", ylab="mm", xlab="years")
```



In conclusion, individual children have different baseline PPMF distances. Girls tended to have a higher PPMF distance at birth. However, boys have a faster growth rate than girls.

Note on lme4 package

Mixed effects modeling is a fast moving subject. A new package in **R** version 2.4.1, called `lme4,` was introduced. The package contains a function called `lmer`, which is more efficient than the `glmmPQL` function in the **`MASS`** package and can accommodate more complicated types of nesting. For example, analysis of clinical visits could be simultanesouly nested both by patient and by physician. While this feature is more advanced than what has been demonstrated in this chapter, this new package gives similar results for simple nesting. However, it is still in the experimental stage. For example, fitted values cannot be easily obtained. When this package is fully developed, it may replace the contents of this chapter.

References

Pinheiro, J. C. & Bates, D. M. 2000. Mixed-Effects Models in S and S-PLUS. New York: Springer.

Raudenbush, S. W. & Bryk, A. S. 2002. Hierarchical Linear Models: Applications and Data Analysis Methods. 2nd ed. Thousand Oaks CA: Sage.

Exercises

The dataset **Bang** consists of a subset of data from the '1988 Bangladesh Fertility Survey'.

```
> zap()
> data(Bang)
> use(Bang)
> label.var(woman, "woman ID")

# Response variable
> label.var(user, "current contraceptive use")
> label.var(age_mean, "age(yr) centred around mean")
> living.children <- factor(living.children)
> label.var(living.children, "No. of children living")
```

Problem 1.

Use `glmmPQL` to compute the effects of the number of living children, age and living in urban area on the probability of contraceptive use among the women. Compute the 95% confidence interval of their odds ratios.

Problem 2.

Does number of living children have a linear dose response relationship with contraceptive use?

Problem 3.

Should age be a random effect?

Problem 4.

Does age have the same effect among urban and rural women on contraceptive use?

Chapter 21: Survival Analysis

In a cohort study, a person is followed up from a starting time to the end of the study or to the time the follow-up has been terminated by the outcome event, whichever comes first. The event-free duration is an important outcome. For an unwanted event, the desired outcome is a longer event-free duration.

For subjects whose events take place before the end of the study, the total duration of time is known. For the subjects whose follow up times end without the event, the end status is called 'censored' because the actual duration of time to the event is not known or 'censored' by the study. The outcome variable for each subject is therefore composed of 'time' and the 'status' at the end. Mathematically, the status is 1 if the event takes place and 0 otherwise.

Example: Age at marriage

A data management workshop was carried out in 1997. Each of the 27 participants was asked to provide personal information on their sex, birth year, education level, marital status and year of marriage (for those who were married). The objective of this analysis is to use survival analysis methods to examine this dataset.

```
> library(survival)
> data(Marryage)
> use(Marryage)
> des()

No. of observations =27

  Variable      Class           Description
1 id            integer
2 sex           factor
3 birthyr       integer         year of birth
4 educ          factor          level of eduction
5 marital       factor          marital status
6 maryr         integer         year of marriage
7 endyr         integer         year of analysis

> summ()

No. of observations = 27
```

```
  Var. name Obs.  mean    median  s.d.   min.   max.
1 id        27    14      14      7.94   1      27
2 sex       27    1.667   2       0.48   1      2
3 birthyr   27    1962.15 1963    6.11   1952   1972
4 educ      27    1.519   2       0.509  1      2
5 marital   27    1.593   2       0.501  1      2
6 maryr     16    1987.56 1988    5.18   1979   1995
7 endyr     27    1997    1997    0      1997   1997
```

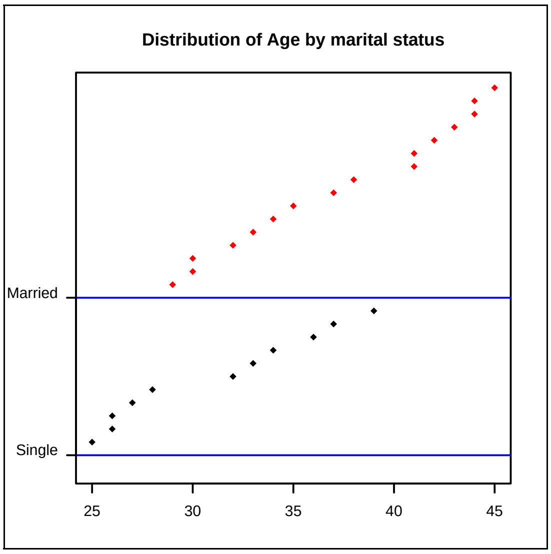
To see the codes for the factor variables type the following command:

```
> codebook()

id       :
  obs. mean   median  s.d.   min.   max.
  27   14     14      7.94   1      27

 ==================
sex      :
Label table: sexlab
       code Frequency Percent
male      1         9    33.3
female    2        18    66.7

 ==================
birthyr          :       year of birth
  obs. mean     median  s.d.   min.   max.
  27   1962.148 1963    6.11   1952   1972

 ==================
educ     :       level of education
Label table: educlab
          code Frequency Percent
bach-        2        13    48.1
>bachelor    3        14    51.9

 ==================
marital          :       marital status
Label table: marlab
        code Frequency Percent
Single     1        11    40.7
Married    2        16    59.3

 ==================
maryr    :       year of marriage
  obs. mean     median  s.d.   min.   max.
  16   1987.562 1988    5.18   1979   1995

 ==================
endyr    :       year of analysis
  obs. mean   median  s.d.   min.   max.
  27   1997   1997    0      1997   1997
 ==================
```

Note that the original codes for the variable 'educ' were 2 = bach-, 3 = >bachelor, as shown in the output of the *codebook* command. This was how the codes were defined in the original data entry program, and the label table associated with each categorical variable were kept with the data. In the output from the *summ* function however, the numeric codes for 'educ' are displayed as 1 (bach-) and 2 (>bachelor). This anomaly is simply due to unclassing the levels of the factor variable in the output from the *summ* command. When R converts something to a factor the first level will always have an underlying code of 1. These numeric codes should not be confused with the original coding scheme. In fact, the codes were only used during the original entry of the data, and are never used during data analysis.

The variable 'endyr', fixed at 1997, is used for computation of age and age at marriage.

```
> age <- endyr - birthyr
> label.var(age, "Age")
> summ(age, by = marital)
For marital = Single
  Obs.    mean    median  s.d.   min.    max.
  11      31.18   32      4.996  25      39

For marital = Married
  Obs.    mean    median  s.d.   min.    max.
  16      37.38   37.5    5.596  29      45
```



There were 16 (59%) married participants. Clearly the married participants were older than the single ones.

```
> age.marr <- maryr - birthyr
> label.var(age.marr, "Age at marriage")
> summ(.data[,8:9])

No. of observations = 27

  Var. name  obs. mean   median  s.d.   min.   max.
1 age        27   34.85  34      6.11   25     45
2 age.marr   16   27.94  27.5    2.77   25     36
```

Among the 16 married participants the mean age at marriage was 27.94 years.

The whole essence of survival analysis is related to “time-to-event”. In this dataset we are using age as the time variable and marriage as the event. In most epidemiological studies 'time' is usually considered to be duration of follow up and the event is usually occurrence of an unwanted event, such as death or disease recurrence. Our data comes from a cross-sectional survey, whereas most data for survival analysis come from follow up studies. However, the procedures used on this simple dataset can be applied to other survival type data.

Survival object in R

The **survival** library contains all the functions necessary to analyse survival type data. In order to analyse this data, we need to create an object of class *Surv*, which combines the information of time and status in a single object. The status variable must be either numeric or logical. If numeric, there are two options. Values must be either 0=censored and 1=event, or 1=censored and 2=event. If logical, FALSE=censored and TRUE=event. In the **Marryage** dataset, 'marital' is a factor and so must be converted to one of the formats specified above. We will choose the logical format, but this is arbitrary.

```
> married <- marital == "Married"
> time <- ifelse(married, age.marr, age)
```

Note that time for married and unmarried subjects are generated differently. For a married person, we know exactly that the duration of time is their age at marriage. Their survival time stops at the year of marriage. For an unmarried person, we do not know this length of time. So their current age is used instead.

The survival object for marriage can now be created and compared against other variables.

```
> (surv.marr <- Surv(time, married))
[1] 26  26  29  25+ 26  26+ 28  28  28  36+ 36  39+ 29  33+
[15] 25  31  27  34+ 37+ 26  27+ 25  27  26+ 28+ 30  32+

> head(data.frame(age, age.marr, married, surv.marr))
```

```
  age age.marr married surv
1  44       26    TRUE   26
2  43       26    TRUE   26
3  45       29    TRUE   29
4  25       NA   FALSE   25+
5  37       26    TRUE   26
6  26       NA   FALSE   26+
```

For the first three subjects, and the 5th, who were all married, the values of 'surv.marr' are equal to their age at marriage. For the 4th and the 6th subjects, the values are equal to their current age. The plus sign indicates that the actual 'time' is beyond those values but were censored. Those participants had not married at the time of the workshop.

For further exploration, subsets of variables sorted by 'time' are displayed by the following command.

```
> cbind(age, sex, age.marr, married, surv.marr)[order(time),]
      age sex age.marr married time status
 [1,]  25   1       NA       0   25      0
 [2,]  32   2       25       1   25      1
 [3,]  29   1       25       1   25      1
 [4,]  44   1       26       1   26      1
 [5,]  43   2       26       1   26      1
 [6,]  37   2       26       1   26      1
 [7,]  26   2       NA       0   26      0
 [8,]  34   1       26       1   26      1

======== subsequent lines omitted ========
```

The 'Surv' object consists of both 'time' and 'status'. The first person, a 25 year old male, was single. His time is 25 and his status is 0, i.e. his event is censored. The second person was a 32 year old woman who had married at age 25, so this is her time. The event (marriage) had already occurred, thus her status = 1, etc.

Life table

A life table is a tabulation of the survival, event and survival probability over time. The classical method for this analysis in the general population has been well developed for centuries. In general, the method involves calculating the cumulative survival probability, which is the product of the survival probabilities at each step. For our simple dataset, the overall life table can be achieved by:

```
> fit <- survfit(surv.marr)
> summary(fit, censor=TRUE)
Call: survfit(formula = surv.marr)
 time n.risk n.event survival std.err lower95CI upper95CI
   25     27       2    0.926  0.0504     0.832     1.000
   26     24       4    0.772  0.0820     0.627     0.950
   27     18       2    0.686  0.0926     0.526     0.894
   28     15       3    0.549  0.1025     0.380     0.791
   29     11       2    0.449  0.1054     0.283     0.711
   30      9       1    0.399  0.1048     0.238     0.668
   31      8       1    0.349  0.1029     0.196     0.622
   32      7       0    0.349  0.1029     0.196     0.622
   33      6       0    0.349  0.1029     0.196     0.622
   34      5       0    0.349  0.1029     0.196     0.622
   36      4       1    0.262  0.1080     0.117     0.588
   37      2       0    0.262  0.1080     0.117     0.588
   39      1       0    0.262  0.1080     0.117     0.588
```

The first row of the output says that at time 25 (when all participants were aged 25 - which is everyone), there were 27 subjects, two of whom were married at that time. The survival probability (probability of getting married at this age) is calculated as (27-2)/27 = 0.926. In fact, there is one person aged 25 years who is not shown. This person is censored (not married) so is included in this row but not in subsequent rows.

On the second row, there were 24 persons remaining who had reached or passed their 26th birthday (27 started, 2 events and 1 censored at the end of the 25th year). At this time, 4 events took place, and since the third row says that only 18 persons remained at the next time point, 2 subjects must have been censored. The survival probability for time 26 is therefore (24 - 4)/24 = 0.833. When multiplying this value with the previous probability in the first row, the cumulative probability is (25/27) x (20/24) = 0.772. This computation of cumulative survival probability continues in a similar way until the end of the dataset. Note that at the time points of 32, 33, 34, 37 and 39 years, there were no events (n.event = 0). The probabilities are therefore unchanged.

The above Kaplan-Meier life table is a slight modification from the classical demographical method where the time interval is fixed (usually at every 5 years of age) and adjustment for incomplete information of exact time of event is taken into account.

Kaplan-Meier curve

The summary of a survival object reveals many sub-objects.

```
> km1 <- summary(fit, censor=T)
> attributes(km1)
$names
[1] "surv"     "time"     "n.risk"   "n.event"  "conf.int"
  "std.err"  "lower"    "upper"    "call"
$class
[1] "summary.survfit"
```

We can use this 'km1' object to plot 'time' vs 'surv', to produce a stepped line plot, which is called a survival curve or 'Kaplan-Meier curve'.

```
> plot(km1$time, km1$surv, type="s")
```

If 'xlim=c(25, 40)' is added to the command, the curve will be very similar to that produced by the standard command.

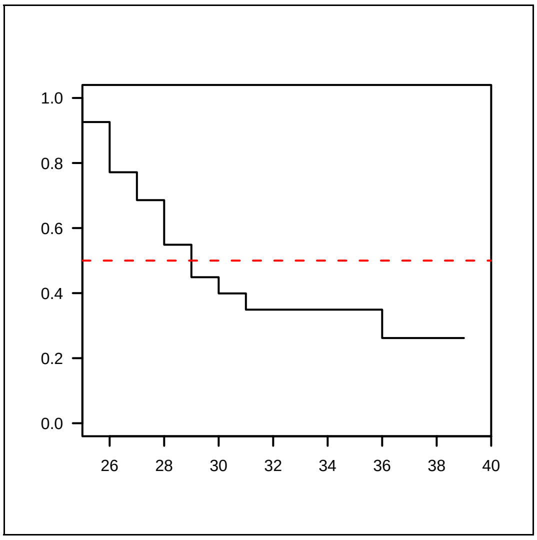
```
> plot(fit, xlim=c(25, 40))
```

When there is only one curve plotted, the two 95% confidence interval lines and the time marks for censored subjects are included in the plot. To suppress them, they can be set be FALSE.

```
> plot(fit, conf.int=F, mark.time=F, xlim=c(25, 38), las=1)
```

The vertical axis is survival probability and the horizontal axis is time. If a horizontal line were drawn at probability 50%, it would cross the survival curve at the point of the median survival time. If less than half of the subjects have experienced the event then the median survival time is undefined.

```
> abline(h=.5, lty=2, col="red")
```



In this dataset, the median survival time (age at marriage) is 29 years. This value is actually displayed when the '`fit`' object is typed.

```
> fit
Call: survfit(formula = surv.marr)

      n  events  median 0.95LCL 0.95UCL
     27      16      29      27      36
```

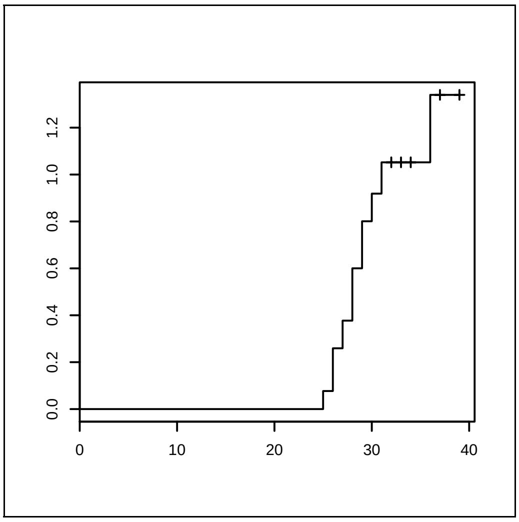
The numbers at risk at various time points can also be displayed on the plot.

```
> stimes <- seq(from=20, to=40, by=5)
> sfit <- summary(fit, times = stimes)
> sfit
Call: survfit(formula = surv.marr)

 time n.risk n.event survival std.err lower95%CI upper95% CI
   20     27       0    1.000  0.0000      1.000       1.000
   25     27       2    0.926  0.0504      0.735       0.981
   30      9      12    0.399  0.1048      0.200       0.592
   35      4       1    0.349  0.1029      0.162       0.545

> n.risk <- sfit$n.risk
> n.time <- sfit$time
> mtext(n.risk, side=1, line=2, at=stimes, cex=0.8)
```

Cumulative hazard rate

The hazard rate is the proportion of failures per unit time. In epidemiological studies, the rate can vary considerably over time. Graphically, it is better to draw the cumulative rate since it is relatively easy to perceive the change of rate by the slope of the cumulative curve.

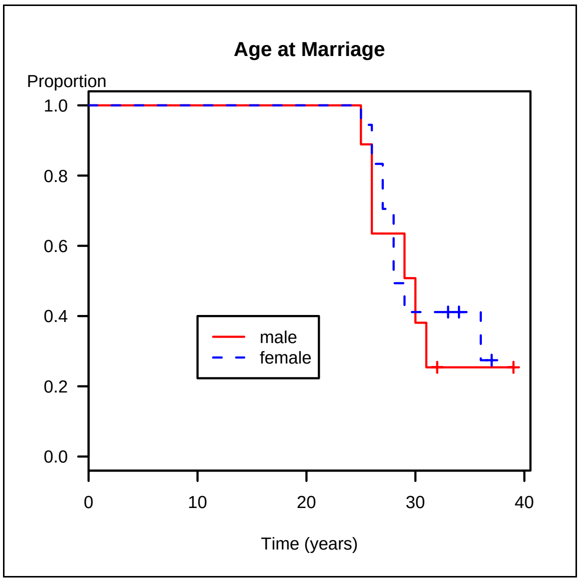
```
> plot(fit, conf.int=FALSE, fun="cumhaz")
```



In the first 25 years, the slope is flat due to the absence of events. From 25-31 years, the slope is relatively steep, indicating a high rate of marriage during these years. The last steep rise occurs at 36 years. At the end of curve, the rate is not very precise due to the smallness of the sample size in this time period.

Survival summaries can be obtained by different levels of a factor variable by adding terms to the formula argument of the `survfit` function. Multiple survival curves can also be shown in the same graph.

```
> fit <- survfit(surv.marr ~ sex)
> fit
Call: survfit(formula = surv.marr ~ sex)

            n events median 0.95LCL 0.95UCL
sex=male    9      6     30      26     Inf
sex=female 18     10     28      28     Inf

> summary(fit)

Call: survfit(formula = surv.marr ~ sex)

                sex=male
time n.risk n.event survival std.err lower 95%CI upper 95%CI
  25      9       1    0.889   0.105       0.706       1.000
  26      7       2    0.635   0.169       0.377       1.000
  29      5       1    0.508   0.177       0.257       1.000
  30      4       1    0.381   0.172       0.157       0.924
  31      3       1    0.254   0.155       0.077       0.838

                sex=female
time n.risk n.event survival std.err lower 95%CI upper 95%CI
  25     18       1    0.944  0.0540      0.8443       1.000
  26     17       2    0.833  0.0878      0.6778       1.000
  27     13       2    0.705  0.1117      0.5169       0.962
  28     10       3    0.494  0.1287      0.2961       0.823
  29      6       1    0.411  0.1309      0.2204       0.768
  36      3       1    0.274  0.1419      0.0994       0.756

> plot(fit, col=c("red", "blue"), lty=c(1,2), las=1)
> title(main="Age at Marriage", xlab="Time (years)")
> mtext(side=3, text="Proportion", at=-2)

> legend(10,.4, legend=c("male", "female"), lty=c(1,2),
    col=c("red", "blue"))
```



When there are multiple survival curves, the 95% confidence interval lines are omitted. The curves appear very similar, indicating that both the males and females in the workshop married at similar rates. More formal comparison among groups is explained in detail in the next section.

Statistical comparison among survival curves

Survival curves can be tested for statistical difference with the `survdiff` command.

```
> survdiff(surv.marr ~ sex)
Call:
survdiff(formula = surv.marr ~ sex)

            N Observed Expected (O-E)^2/E (O-E)^2/V
sex=male    9        6     5.37    0.0746     0.125
sex=female 18       10    10.63    0.0376     0.125

 Chisq= 0.1  on 1 degrees of freedom, p= 0.724
```

With this small sample size, the difference can simply be explained by chance alone. The `survdiff` command actually has 5 arguments, the last one being 'rho', which specifies the type of test to use. When rho = 0 (by default) the log-rank or Mantel-Haenszel chi-squared test is performed. This compares the expected number of events in each group against the observed values. If the level of difference between these two groups is too high, the chi-squared value will be high and the P value will be small indicating that the curves are significantly different. If rho = 1 then the Peto modification of the Gehan-Wilcoxon test (sometimes called the Peto test) is performed, which places more weight on earlier events.

Stratified comparison

There is a significant association between sex and education.

```
> cc(sex, educ)
        educ
sex      bach- >bachelor Total
  male       1         8     9
  female    12         6    18
  Total     13        14    27
OR =  0.07
95% CI = 0.001 0.715
Chi-squared = 7.418 ,  1 d.f. , P value = 0.006
Fisher's exact test (2-sided) P value = 0.013
```

Females are seen to have a higher level of education. The effect of sex on survival with adjustment for education can be obtained as follows:

```
> survdiff(surv.marr ~ sex + strata(educ))
Call:
survdiff(formula=surv.marr ~ sex + strata(educ))

            N Observed Expected (O-E)^2/E (O-E)^2/V
sex=male    9        6     5.61    0.0266    0.0784
sex=female 18       10    10.39    0.0144    0.0784

 Chisq= 0.1  on 1 degrees of freedom, p= 0.779
```

The adjusted effect is not much different from the crude one. Lack of confounding in this case is due to the lack of independent effect of education on age of marriage.

We will keep this working environment and return to work on it in the next chapter.

```
> save.image(file = "Marryage.Rdata")
```

References

Kleinbaum D, Klein M (2005). Survival Analysis: A Self-Learning Text.

Hosmer Jr D, Lemeshow S (1999). Applied Survival Analysis: Regression Modeling of Time to Event Data.

Exercises

The dataset **`Compaq`** contains data from a follow up study on breast cancer in Europe evaluating whether patients in private hospital ('hospital') had better survival ('year').

Problem 1.

Check the distribution of year of deaths and censoring.

Problem 2.

Draw Kaplan-Meier curves for each hospital group with censoring marks shown on the curves. Display the numbers at risk at reasonably spaced time intervals.

Problem 3.

Test the significance with and without adjustment for other potential confounders: age ('agegr'), stage of disease ('stage') and socio-economic level ('ses').

Chapter 22: Cox Regression

Cox's proportional hazard model

Similar to other types of outcome variables, survival outcomes can be tested for more than one predictor using regression modelling. There are many 'parametric regression' choices for the survival object. Each of them has a specific assumption about the distribution of the survival probability over time (so called hazard function). In epidemiological studies, the most popular regression choice for survival analysis is Cox regression, which has no assumption regarding the hazard function.

While parametric regression models allow prediction of the probability of survival at each point of time, Cox regression focuses on testing for differences of survival probability among groups with adjustment for confounding factors. The only important assumption it adheres to is 'proportional hazards'.

Mathematically, the hazard rate *h=h(t)* is a function of (or depends on) say, *n* independent covariates ***X***, where ***X*** denotes the vector $X_1, X_2, X_3 \ldots , X_n$ each of which is X_i, i = 1, 2, 3,…*n*, and *t* is time. The hazard function can also be written as *h(t,* ***X****)*. This denotes that the summation of influences of one group over the other is a fixed proportion.

Under the proportional hazards assumption:

$$h(t,X) = h_0(t)e^{\sum \beta_i X_i}$$

The left-hand side of the equation says that the hazard is influenced by time and the covariates. The right-hand side of the equation contains $h_0(t)$, which is the baseline hazard function when all the X_i are zero. This baseline hazard function is multiplied by e to the power of the summation of all the covariates weighted by the estimated coefficients, β_i.

Consequently,

$$\frac{h(t,X)}{h_0(t)} = e^{\sum \beta_i X_i}$$

The left-hand side is the proportion, or ratio, between the hazard of the group with exposure of ***X*** against the baseline hazard. The right-hand side is the exponentiation of the sum of products of estimated coefficients and the covariate vector, X_i, which is now independent of time, i.e. assumed constant over time. Thus $e^{\beta iXi}$ is the increment of the hazard, or hazard ratio, due to the independent effect of the i^{th} variable.

Whenever there is an event, the conditional probability, or proportion of subjects among different groups in getting the hazard, is assumed constant.

We will use the data from the preceding chapter to examine the independent effect of sex on the age of marriage.

```
> zap()
> library(survival)
Loading required package: splines
> load("Marryage.Rdata")
> use(.data)
> cox1 <- coxph(surv.marr ~ sex)
> cox1
===============================
            coef exp(coef) se(coef)      z    p
sexfemale -0.170     0.844    0.522 -0.325 0.74
```

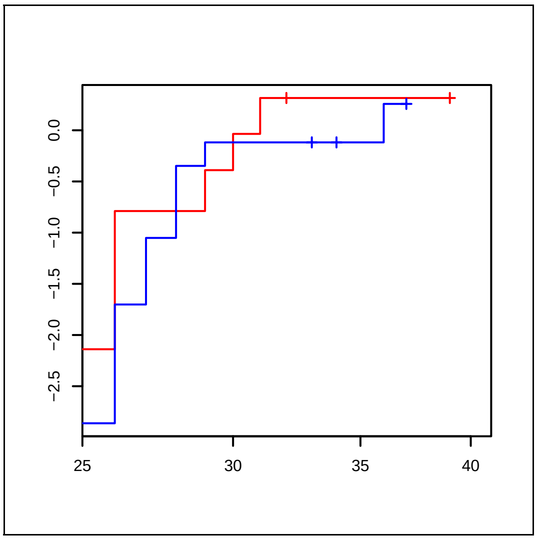
The coefficient is negative and non-significant. The hazard ratio, exp(coef), is 0.844 suggesting an overall reduction of 16% hazard rate of females compared to males. To obtain its 95% confidence interval, a summary of this 'coxph' object is necessary.

```
> summary(cox1)
===============================
          exp(coef) exp(-coef) lower .95 upper .95
sexfemale     0.844       1.19     0.304      2.35
===============================
```

Testing the proportional hazards assumption

Graphically, the curves of the two sexes can be compared after the vertical axis has been transformed by -log(log(y)) and plotted against log(time). If the two curves are parallel, the proportional hazards assumption is unlikely to be violated.

```
> fit <- survfit(surv.marr ~ sex)
> plot(fit, conf.int=FALSE, fun="cloglog", xlim=c(25,41),
    col=c("red", "blue"))
```



The two curves cross more than once. It is difficult to judge from the graph whether the assumption has been violated. A formal test of the proportional hazards assumption can be carried out as follows:

```
> cox.zph(model1) -> diag1; diag1
              rho    chisq     p
sexfemale 0.00756 0.000883 0.976
```

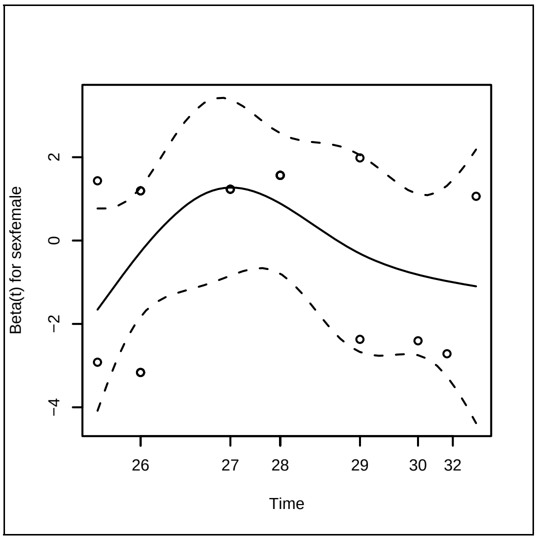
The evidence against the proportional hazards assumption is very weak. This diagnostic result can be further explored.

Time trend of the hazard ratio

These attributes can be summarised in a graph by plotting the change of beta, the estimated coefficients, over time.

```
> diag1$x  # x coordinates for plotting time
> diag1$y  # y coordinates for plotting beta coefficients
> plot(cox.zph(model1))
```

This graph should be read along with the previous results earlier in the chapter where the events and the information of sex of the subjects are sorted by time.



```
> data.frame(age, sex, age.marr, married,
    surv.marr)[order(time),]
   age    sex age.marr married surv.marr
4   25   male       NA   FALSE       25+
15  32 female       25    TRUE       25
22  29   male       25    TRUE       25
1   44   male       26    TRUE       26
2   43 female       26    TRUE       26
========================================
```

The first two events occurred in the 25th year where one male and one female got married. The hazard in 'diag1$y' is 1.43 and -2.92. In the 26th year, there were four events of two males (beta = -3.16) and two females (beta = 1.19). The duplicate values of beta result in a warning but this is not serious. Subsequent points are plotted in the same fashion. A line is drawn to pass through these betas to illustrate the level of stability of the coefficient over time. The probability of getting married for females is lower than for males when they are younger than 26 years or older than 29 years. In between, females have a higher probability of getting married. However, the test suggests that this finding can be simply explained by chance alone.

For multiple covariates the same principle applies.

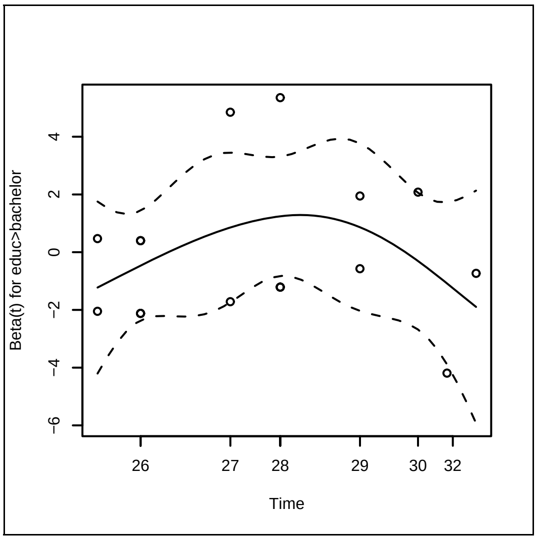
```
> cox2 <- coxph(surv.marr ~ sex + educ)
> cox2
> summary(cox2)
===================================================
             exp(coef) exp(-coef) lower.95 upper.95
sexfemale        0.831       1.20    0.230     2.99
educ>bachelor    0.975       1.03    0.278     3.42
===================================================
> cox.zph(cox2) -> diag2; diag2
                   rho   chisq     p
sexfemale      0.0246 0.00885 0.925
educ>bachelor 0.0321 0.01547 0.901
GLOBAL             NA 0.01604 0.992
```

The test results are separated by each variable. Finally, a global test is performed showing a non-significant result.

```
> diag2$x # x coordinates for plotting time: same as diag1
> diag2$y # two columns, one for each variable
> plot(cox.zph(cox2), var=1) # for the first variable of y
```

The coefficients of sex with adjustment for education were not much changed.

```
> plot(cox.zph(cox2), var=2)
```



The hazard rate for marriage of persons who had a higher education rises at around 27-29 years. By the late twenties, they have a slightly higher chance of getting married than those with a lower education. The reverse is true for the remaining times. Again, these differences are not significant and can be explained by chance alone.

Stratified Cox regression

The above example had very few subjects, and not surprisingly the results were not significant. We now revisit the cancer dataset **Compaq**, which was used as the exercise at the end of the preceding chapter. The main aim now is to test whether breast cancer patients in private and public hospitals had different survival rates after adjusting for stage, socio-economic status and age.

```
> zap()
> data(Compaq)
> use(Compaq)
> des(); summ(); codebook()
> surv.ca <- Surv(year, status)
> cox3 <- coxph(surv.ca ~ hospital + stage + ses + agegr)
> summary(cox3)
Call:
coxph(formula=surv.ca ~ hospital+stage+ses+agegr)
  n= 1064
                   coef exp(coef) se(coef)      z       p
hospitalPrivate  -0.4224     0.655    0.142 -2.971 3.0e-03
stageStage 2      0.7682     2.156    0.123  6.221 5.0e-10
stageStage 3      2.4215    11.263    0.156 15.493 0.0e+00
stageStage 4      1.3723     3.944    0.190  7.213 5.5e-13
sesHigh-middle   -0.0944     0.910    0.133 -0.712 4.8e-01
sesPoor-middle    0.0341     1.035    0.178  0.192 8.5e-01
sesPoor          -0.4497     0.638    0.144 -3.126 1.8e-03
agegr40-49        0.2574     1.294    0.164  1.569 1.2e-01
agegr50-59        0.4923     1.636    0.164  2.999 2.7e-03
agegr60+          1.4813     4.399    0.159  9.343 0.0e+00
```

Patients in private hospitals have two-thirds the risk (hazard) compared to those in public hospitals after adjustment for stage, socio-economic status and age. To check whether all three categorical variables deserve to be included in the model, the command `step`, meaning stepwise regression, can be used.

```
> step(cox3)
Start:  AIC= 4854.56
 surv.ca ~ hospital + stage + ses + agegr

           Df    AIC
<none>        4854.6
- ses       3 4860.2
- hospital  1 4862.0
- agegr     3 4951.6
- stage     3 5059.9
===== Further output omitted due to redundancy ====
```

The level of AIC is lowest when none of the variables is removed. Therefore, all should be kept. Next the proportional hazards assumption is assessed.

```
> cox.zph(cox3)
                              rho   chisq       p
hospitalPrivate hospital  0.03946  0.6568 0.41768
stageStage 2              0.05406  1.1629 0.28086
stageStage 3             -0.09707  3.6786 0.05512
stageStage 4             -0.10222  4.2948 0.03823
sesHigh-middle            0.00968  0.0367 0.84818
sesPoor-middle           -0.04391  0.7612 0.38297
sesPoor                   0.10409  4.4568 0.03476
agegr40-49               -0.07835  2.3831 0.12266
agegr50-59               -0.09297  3.2339 0.07213
agegr60+                 -0.09599  3.5242 0.06048
GLOBAL                         NA 23.3117 0.00965
```

The highest stage and the lowest socio-economic group contribute the most to the chi-squared statistic. The global test gives a significant P value suggesting that the assumption is violated. A possible solution is to do a stratified analysis on one of the categorical variables, say 'stage'.

```
> cox4 <- coxph(surv.ca ~ hospital+strata(stage)+ses+agegr)
> cox.zph(cox4)
                              rho  chisq      p
hospitalPrivate hospital  0.04407  0.797 0.3720
sesHigh-middle            0.00801  0.025 0.8743
sesPoor-middle           -0.04857  0.920 0.3376
sesPoor                   0.09747  3.785 0.0517
agegr40-49               -0.07366  2.097 0.1476
agegr50-59               -0.08324  2.565 0.1093
agegr60+                 -0.08521  2.761 0.0966
GLOBAL                         NA 10.297 0.1724
```

Using 'stage' as a stratification factor reduces all chi-squared values and the proportional hazards assumption is now not violated.

```
> summary(cox4)
Call:
coxph(formula = surv.ca ~ hospital + strata(stage) + ses + 
  agegr)
  n= 1064
                     coef exp(coef) se(coef)      z      p
hospitalPrivate   -0.4049     0.667    0.141 -2.866 0.0042
sesHigh-middle    -0.1078     0.898    0.133 -0.811 0.4200
sesPoor-middle     0.0374     1.038    0.179  0.209 0.8300
sesPoor           -0.4201     0.657    0.144 -2.926 0.0034
agegr40-49         0.2532     1.288    0.164  1.542 0.1200
agegr50-59         0.4703     1.600    0.165  2.857 0.0043
agegr60+           1.4514     4.269    0.159  9.141 0.0000
```

The coefficients of '`cox4`' are quite similar to '`cox3`'. Note the omission of the 'stage' terms. Stratified Cox regression ignores the coefficients of the stratification factor. Since our objective is to document the difference between types of hospital, the coefficients for other variables are not seriously required if the covariates are well adjusted for.

References

Kleinbaum D, Klein M (2005). Survival Analysis: A Self-Learning Text.

Hosmer Jr D, Lemeshow S (1999). Applied Survival Analysis: Regression Modeling of Time to Event Data.

Exercises

Problem 1.

Could the other 2 variables (socio-economic status and age) be used as a stratification factor?

Problem 2.

Use the command `plot(cox.zph)` for '`cox3`' and '`cox4`' to check the change of hazard ratio of private hospital over time. Discuss the pattern of residuals.

Chapter 23 Analysing Attitudes Data

The 'Attitudes' dataset

Although a study on attitudes is in the field of social sciences, an epidemiologist should have some idea on the elementary methods of analysis of this kind of data. A questionnaire on attitudes usually contains questions where the respondents specify their level of agreement to a statement. These levels are often referred to as a Likert scale. Traditionally a five-point scale is used; however seven and even nine-point scales can also be used. Although mostly used in the field of psychometrics, this kind of rating scale is sometimes used in epidemiological studies such as those involving quality of life.

Epicalc offers the *`tableStack`* function to display the distribution of the score of several variables that have the same rating scale. It also detects the items that need to be reversed before the scores of the items are summed or averaged.

The **`Attitudes`** dataset comes from a survey on attitudes related to services among hospital staff. Its details can be sought from the following commands.

```
> help(Attitudes)
> data(Attitudes)
> use(Attitudes)
> des()
> summ()
```

To obtain a compact summary of each questionnaire item simply type:

```
> tableStack(qa1:qa18)
     1  2  3  4  5  count mean sd  description
qa1  0  0  7  54 75 136   4.5  0.6 I have pride in my job
qa2  0  2  13 60 61 136   4.3  0.7 I'm happy to give service
qa3  30 52 25 20 9  136   2.5  1.2 I feel difficulty in giving service
qa4  0  0  10 90 36 136   4.2  0.6 I can improve my service
qa5  0  3  5  39 89 136   4.6  0.7 A service person must have patience
qa6  17 19 58 29 12 135   3    1.1 I would change my job if given ...
qa7  0  3  7  68 58 136   4.3  0.7 Devoting some personal time will...
qa8  0  5  20 59 52 136   4.2  0.8 Hard work will improve oneself
qa9  0  0  4  41 91 136   4.6  0.5 Smiling leads to trust
qa10 1  1  16 74 44 136   4.2  0.7 I feel bad if I cannot give service
```

```
qa11 6  20 35 52 23 136   3.5  1.1 A client is not always right
qa12 2  26 45 49 13 135   3.3  0.9 Experienced clients should not ...
qa13 13 54 37 22 10 136   2.7  1.1 A client violating the regulation..
qa14 0  13 45 62 16 136   3.6  0.8 Understanding colleagues will ...
qa15 0  2  18 82 33 135   4.1  0.7 Clients like this place due to ...
qa16 36 53 21 16 8  134   2.3  1.2 Clients who expect our smiling ...
qa17 4  41 32 44 14 135   3.2  1.1 Clients are often self-centred
qa18 2  1  13 87 33 136   4.1  0.7 Clients should be better served
  Total score         130   67.1 4.9
  Average score       130   3.7  0.3
```

All the items share the same response scale ranging from 1 to 5 although we can see from the output that some items have a zero count for scales 1 and 2. The *tableStack* function determines the minimum and maximum values of the all the variables selected. These can easily be changed by modifying the 'minlevel' and 'maxlevel' arguments to the function, which are set to "auto" by default. Four statistics are computed for each variable: counts, means and standard deviations are presented by default, while medians are also available but must be set to TRUE if wanted. Other arguments include 'var.labels', which controls the display of variable descriptions, and 'total', which controls the appearance of the total and average scores at the bottom.

The total and average scores are not appropriate if any of the items need to be reversed. One can guess the items to reverse based on the wording of the question and to a lesser extent by the reversed distribution compared to the other items. The items to reverse can be specified with the argument 'vars.to.reverse'. For example, if items 3, 6 and 16 are considered to be scaled in the reverse direction to the other items, then these three items should be specified in the 'vars.to.reverse' argument as follows:

```
> tableStack(qa1:qa18, vars.to.reverse=c(qa3,qa6,qa16))
               Reversed 1  2  3  4  5  count mean sd
qa1                .    0  0  7  54 75 136   4.5  0.6
qa2                .    0  2  13 60 61 136   4.3  0.7
qa3                x    9  20 25 52 30 136   3.5  1.2
qa4                .    0  0  10 90 36 136   4.2  0.6
qa5                .    0  3  5  39 89 136   4.6  0.7
qa6                x    12 29 58 19 17 135   3    1.1
qa7                .    0  3  7  68 58 136   4.3  0.7
qa8                .    0  5  20 59 52 136   4.2  0.8
qa9                .    0  0  4  41 91 136   4.6  0.5
qa10               .    1  1  16 74 44 136   4.2  0.7
qa11               .    6  20 35 52 23 136   3.5  1.1
qa12               .    2  26 45 49 13 135   3.3  0.9
qa13               .    13 54 37 22 10 136   2.7  1.1
qa14               .    0  13 45 62 16 136   3.6  0.8
qa15               .    0  2  18 82 33 135   4.1  0.7
qa16               x    8  16 21 53 36 134   3.7  1.2
qa17               .    4  41 32 44 14 135   3.2  1.1
qa18               .    2  1  13 87 33 136   4.1  0.7
 Total score                           130   69.6 5.9
 Average score                         130   3.9  0.3
```

Reversed items are shown with a cross (x) in the column titled "Reversed", indicating that the scale has been reversed for that item. The statistics for the total and average scores will likely change due to the reversed direction of scale of those items. An alternative way to select the items to reverse is to set the 'reverse' argument to TRUE.

```
> tableStack(qa1:qa18, reverse=TRUE)
```

The function will compute the correlation between each score of an item against a weighted average score of all the remaining ones. Items that are negatively correlated with this average will be automatically reversed. In the **`Attitudes`** dataset, these are items 3, 6, 12, 13, 16 and 17.

tableStack for logical variables and factors

All questions in the Attitudes dataset are integers, making it possible to obtain the statistics for each item as well as those for the total score and grand mean. If the classes of the variables are not numeric, only the frequency counts are shown. Let's explore the **`Oswego`** dataset, which contains data on 75 persons under investigation for the cause of acute food poisoning after a dinner party.

```
> data(Oswego)
> use(Oswego)
> des()

No. of observations = 75
   Variable      Class           Description
1  age           numeric
2  sex           AsIs
3  timesupper    numeric
4  ill           logical
5  onsetdate     AsIs
6  onsettime     numeric
7  bakedham      logical
8  spinach       logical
9  mashedpota    logical
10 cabbagesal    logical
11 jello         logical
12 rolls         logical
13 brownbread    logical
14 milk          logical
15 coffee        logical
16 water         logical
17 cakes         logical
18 vanilla       logical
19 chocolate     logical
20 fruitsalad    logical
```

```
> tableStack(bakedham:fruitsalad)
           No Yes count
bakedham   29  46    75
spinach    32  43    75
mashedpota 37  37    74
cabbagesal 47  28    75
jello      52  23    75
rolls      38  37    75
brownbread 48  27    75
milk       71   4    75
coffee     44  31    75
water      51  24    75
cakes      35  40    75
vanilla    21  54    75
chocolate  27  47    74
fruitsalad 69   6    75
```

To obtain the percentages, set the 'by' argument to "none".

```
> tableStack(bakedham:mashedpota, by="none")
              Total
bakedham
   No      29(38.7)
   Yes     46(61.3)

spinach
   No      32(42.7)
   Yes     43(57.3)

mashedpota
   No        37(50)
   Yes       37(50)
```

Alternatively, the prevalence of eaters (Yes) could be displayed by setting the 'prevalence' argument to TRUE.

```
> tableStack(bakedham:mashedpota, by="none", prevalence=TRUE)
                        Total
bakedham = Yes
  prevalence     46/75(61.3%)

spinach = Yes
  prevalence     43/75(57.3%)

mashedpota = Yes
  prevalence       37/74(50%)
```

Return to the **Attitudes** data and change all the variables to factors. This is often the case when the choices are labelled during data entry.

```
> data(Attitudes)
> use(Attitudes)
> scales <- list("strongly agree"=1, "agree"=2, "neutral"=3,
  "disagree"=4, "strongly disagree"=5)
> for(i in 4:21){
   .data[,i] <- factor(.data[,i])
   levels(.data[,i]) <- scales
  }
```

The above sequence of commands simply converts the 4th to 21st columns of the data (items 'qa1' : 'qa21') into factors and assigns the values of each item a label corresponding to the elements in 'scales'. These are the levels of the items.

```
> des()
```

All the items should now be factors. Using the *tableStack* function with this new data frame will result in statistics not being shown.

```
> tableStack(qa1:qa18)
```

Note that the columns are now labelled. If summary statistics are desired then one would need to unclass all the variables in the data frame before using the function. If the data frame contains many variables, this would be quite a laborious task. Epicalc has a function to unclass all the variables inside a data frame resulting in the variables being converted to integers, namely *unclassDataframe*.

```
> unclassDataframe(qa1:qa18)
> des()
> tableStack(qa1:qa18, reverse=TRUE)
```

Cronbach's alpha

For this attitude survey data, the next step in the analysis is to calculate the reliability coefficient, namely Cronbach's alpha, which is a measure of the internal consistency of the questionnaire survey. An analysis of attitude survey data would never be accepted by most social science journals unless Cronbach's alpha has been calculated.

In brief, this coefficient reflects the level of correlation among all items of the same scale. Sometimes it is called the reliability coefficient since it reflects the consistency among the items. If the value of this coefficient is too low (say less than 0.7), the scale is considered to have rather low internal consistency, and the total or mean score calculated from these inconsistent items may not properly reflect the domain that the questions are trying to measure.

The function *alpha* from Epicalc calculates Cronbach's alpha, and allows the user to see the effect of removing each item on both the coefficient and the correlation between each item and the remaining ones.

The arguments for the function are similar to the *tableStack* function. The first argument is the vector of variable names (without quotes) or column index of the variables in the data frame.

```
> alpha(qa1:qa18, var.labels=FALSE)
Number of items in the scale = 18
Sample size = 136
Average inter-item correlation = 0.1461

Cronbach's alpha: cov/cor computed with
  'pairwise.complete.obs'
      unstandardized value = 0.708
        standardized value = 0.7549

Item(s) reversed and new alpha if the item omitted:
   Reversed Alpha    Std.Alpha r(item,rest) description
qa1    .    0.685817 0.732773  0.461288     I have pride in my job
qa2    .    0.674703 0.725548  0.556550     I'm happy to give
qa3    x    0.699929 0.749653  0.282889     I feel difficulty in
qa4    .    0.686278 0.730758  0.467432     I can improve my
qa5    .    0.691590 0.739174  0.329396     A service person must
qa6    x    0.682247 0.739252  0.392348     I would change my job
qa7    .    0.674438 0.722168  0.563173     Devoting some personal
qa8    .    0.677646 0.728148  0.484181     Hard work will improve
qa9    .    0.691061 0.736795  0.410533     Smiling leads to trust
qa10   .    0.708569 0.755929  0.153067     I feel bad if I cannot
qa11   .    0.729312 0.764704  0.007361     A client is not always
qa12   x    0.720390 0.765974  0.057229     Experienced clients
qa13   x    0.693353 0.748163  0.303587     A client violating the
qa14   .    0.710688 0.757130  0.128318     Understanding colleagues
qa15   .    0.685665 0.733966  0.415518     Clients like this place
qa16   x    0.692937 0.744674  0.311757     Clients who expect our
qa17   x    0.720186 0.764488  0.088212     Clients are often self…
qa18   .    0.695617 0.744489  0.296922     Clients should be...
```

The function first computes the covariance matrix among all selected variables. This matrix is then used to compute the average of the inter-item correlation.

Secondly, the unstandardized and standardized alpha coefficients are computed based on a formula, which can be found in most textbooks. The unstandardized value is suitable when all items share the same value coding, such as the **Attitudes** dataset where all items have a scale of 1 to 5. The standardized alpha is appropriate when the variables are coded on a different scale, which is less commonly found in a study on attitudes.

Finally, a table is shown, with items that have been automatically reversed marked with an 'x', similar to the *tableStack* command with no 'by' argument given. The columns 'alpha' and 'Std. alpha' are the unstandardized and standardized alpha coefficients, respectively, obtained when each variable is omitted from the computation.

The function also has a 'reverse' argument, the default value being TRUE. If set to FALSE, then the scale of all items are assumed to be measured in the same direction. In this dataset that would result in lower alpha values and most likely to incorrect conclusions.

From the previous output, the unstandardized coefficient is 0.71 and the candidate items that could be removed to improve (increase) the alpha coefficients are items 10, 11, 12, 14 and 17.

Further analysis could be pursued by successive omission of items. A successful selection of items would be to have a questionnaire with not too many items yet with an acceptably high alpha coefficient. Consider removing item 11, since it results in the highest alpha coefficient if it is removed and also has the lowest correlation with all other items.

```
> alpha(c(qa1:qa10, qa12:qa18))
```

Both the unstandardized and standardized alpha coefficients have increased. As indicated by the third section of the results, the alpha coefficients can be further increased by removing item 12.

```
> alpha(c(qa1:qa10, qa13:qa18))
```

and then item 17.

```
> alpha(c(qa1:qa10, qa13:qa16, qa18))
```

and then item 14.

```
> alpha(c(qa1:qa10, qa13, qa15:qa16, qa18))
```

and then item 10.

```
> alpha(c(qa1:qa9, qa13, qa15:qa16, qa18))
```

Further removal of items does not result in any improvement to the alpha coefficients. Altogether, 5 items were removed from the original 18 items to arrive at the best model. This somewhat tedious task can be automated by using another Epicalc function called *alphaBest*.

```
> alphaBest(qa1:qa18)
$best.alpha
[1] 0.7620925

$removed
qa11 qa12 qa17 qa14 qa10
  14   15   20   17   13

$remaining
 qa1  qa2  qa3  qa4  qa5 qa6 qa7 qa8 qa9 qa13 qa15 qa16 qa18
   4    5    6    7    8   9  10  11  12   16   18   19   21
```

The best Cronbach's alpha is achieved with the index of the items removed and the ones remaining listed. The values of these two vectors are the index of the variables in the data frame. For example, we first removed 'qa11', which is the 14th variable, then 'qa12', which is the 15th, 'qa17', which is the 20th, and so on. Similarly, the remaining variables are 'qa1', which the 4th variable, 'qa2', which is the 5th, 'qa3', which is the 6th, etc.

By default, the function selects the best model based on the unstandardized alpha coefficient. If best selection is to be based on the standardized alpha, then 'standardized' should be set to TRUE.

```
> alphaBest(qa1:qa18, standardized=TRUE)
```

The results are exactly the same in this case since all items have the same scale. Saving the removed and the remaining items as an index has a very important advantage as shown next. The vector of 'remaining' items can be saved and further used in the *tableStack* command described previously.

```
> alphaBest(qa1:qa18)$remaining -> wanted
```

The *tableStack* function accepts an integer vector for the 'vars' argument. To get the best final set of items, with necessary reversing, the next step is to use the *tableStack* command on the wanted items saving the results to an **R** object.

```
> tableStack(vars=wanted, reverse=TRUE, var.labels=FALSE) -> b
```

Note that now the mean score has increased from 3.7 to 4.0 using the original (perhaps naïve) method of keeping all items and without investigating the need to reverse items. The saved object 'b' contains the mean and total scores, which can be saved back to the default data frame for further hypothesis testing.

```
> mean.score <- b$mean.score
> total.score <- b$total.score
> pack()
> des()
> t.test(mean.score ~ sex)   # p-value = 0.7348
```

An alternative way of displaying results from hypothesis testing for difference between two genders in the items and mean score would be:

```
> tableStack(vars=c(wanted, mean.score), by=sex, var.=FALSE)
```

The function determines the appropriate statistical test to use for all variables. If the distribution is not normal, then the Wilcoxon rank sum test is used instead of the t-test. Details of the *tableStack* command using the 'by' argument are described in Chapter 27 – "Table Stacking for a Manuscript".

Summary

In summary, when you have a dataset on attitudes, it is a good idea to explore the variables with *tableStack*, initially without any of the items reversed. Have a careful look at the comparative distribution of the items and read each question (or variable description) to get an idea of the direction, either positive or negative, of the item's scale. The items that should be reversed are usually the ones with the distribution contrary to the remaining majority. If the variables are factors, use *unclassDataframe* to convert them to integers. There is actually no need to save the total or mean scores at this stage. Check Cronbach's alpha using the functions *alpha* and subsequently *alphaBest* to get the best subsets of items that maximize alpha. Save the results to an object and put the 'remaining' items as the 'vars' argument to the final *tableStack* command with 'reverse=TRUE'. The total and average scores of the best selected model with items correctly reversed can be saved and ready for further analysis.

References

Cronbach, L. J. 1951. Coefficient alpha and internal structure of tests. *Psychometrika*, 16: 297–334.

Exercise

Download and install the **psy** library from the CRAN website. Load this library and examine the **`expsy`** dataset.

```
> library(psy)
> data(expsy)
> des(expsy)
> head(expsy)
```

Determine which of the items (it1 to it10) need to be reversed. Find the best subset of the items using Cronbach's alpha coefficient.

Chapter 24: Sample size calculation

Sample size calculation is very important for an epidemiological study. For most surveys, the population size is large, consequently the costs involved in collecting data from all subjects would be high. In clinical studies, recruiting too many subjects into the study not only causes management and financial problems but also raises ethical concerns. If a conclusion can be drawn from a small sample size, recruiting more subjects than necessary may pose an unnecessary risk to the group of subjects whose treatment is known to be inferior. On the other hand, a survey with a sample size that is too small will not be able to detect a statistically significant effect if there truly is one.

Functions to calculate sample size

Experimenting with functions to calculate sample sizes will enable new **R** users to understand the principles of arguments more quickly and meaningfully.

Epicalc comes with four functions for sample size calculation. The first one is for a prevalence survey. The second is for comparison of two proportions, which can be for a case-control study, cross-sectional study, cohort study or randomised controlled trial. The third function is used for the comparison of two means. The last one is for lot quality assurance sampling.

In addition to these sample size calculations, there are two functions for computing the power of a comparative study, one for comparing two means, and the other for comparing two proportions.

Field survey

The aim of a field survey is usually to document the prevalence in the population on a certain condition, such as helminthic infection, or coverage of a health service, such as an immunization programme. The sample size required depends on the estimated prevalence and the level of errors of prevalence that the researcher can accept. For many circumstances, cluster sampling is employed. The advantage of this sampling method is that it reduces the time and budget for travelling to collect data.

For example, simple random sampling may require 96 persons from 96 different villages to be surveyed. This can place a heavy burden on the travelling resources. Instead, the number of villages can be reduced to, say, 30 and the sample size compensated by sampling more subjects from each selected village. The slight increase in sample size is more than offset by the large reduction in travelling costs. The cluster sampling technique, however, encounters another problem. People in the same villages often tend to be more similar to each other than from people from other villages in terms of disease risk and coverage of service etc. In other words, subjects selected from the same cluster are usually not 'independent'. Therefore the sample size estimated from a simple random sampling technique must be inflated to cover this 'alikeness among the same cluster' (or 'design effect') problem.

The function `n.for.survey` in Epicalc is used for the calculation of the sample size for a survey. To have a look at the arguments of this function type:

```
> args(n.for.survey)
function(p, delta = 0.5 * min(c(p, 1 - p)), popsize = FALSE,
  deff = 1, alpha = 0.05)
```

The arguments to this function are as follows:

p: The estimated prevalence as a proportion between 0 and 1.

delta: The difference between the estimated prevalence and the margin of the confidence interval. For example, if 'p' is estimated to be 30% but we still accept that the maximum error can result in 50% prevalence, then 'delta' is 0.5 - 0.3 = 0.2. If delta is not given, the default value is set to be a half of either p or 1-p, whichever is the smaller. In general, delta has more influence on the sample size than p. When p is small, delta should be smaller than p. Otherwise, the lower limit of the confidence interval will be negative or the upper limit will be higher than 100%, both of which are invalid. The default value is therefore quite acceptable for a rather low prevalence (say, below 15%) or a rather high prevalence (say, above 80%). If the prevalence is in between these values, then half of p (or 1-p) would be too imprecise. The user should then give a smaller delta.

popsize: Finite population size. This is the population size in which the survey is to be conducted. A small population size will require a relatively smaller sample size. If the value is FALSE, it will be ignored and assumed that the population is very large. Usually when the size exceeds a certain value, say 5000, any further increase in the population would have a rather little effect on the sample size.

deff: The design effect, which is the adjustment factor for cluster sampling as explained above. By definition, for simple random sampling, deff is 1. In cluster sampling with a large cluster size and the level of similarity among subjects in the same cluster is high, deff can be large, and so would the required sample size.

alpha: Probability of a Type I error. In standard situations, alpha is set at 0.05 and the confidence interval of p ± delta is the 95% confidence limit of the prevalence. With higher accuracy demands, for example, a 99% confidence limit, the required sample size will be increased.

If a survey is to be conducted with a small (less than 15%) prevalence, in a large population, all the default values of the arguments can be accepted. The command then becomes:

```
> n.for.survey(p=.05)

Sample size for survey.
Assumptions:
  Proportion       = 0.05
  Confidence limit = 95 %
  Delta            = 0.025 from the estimate.
  Sample size      = 292
```

The function sets the 'alpha' value at 0.05, since it was omitted. Thus the confidence limit is 95%. The argument 'delta' is automatically set to half of 5% or 0.025. The design effect, 'deff', is not given and so set at 1. The population size is assumed to be very large and is thus not used in the calculation of the sample size.

In conclusion, the function suggests that if a 95% confidence limit of 5% ± 2.5% (from 2.5% to 7.5%) is desired for an estimated proportion of 0.05 in a large population, then the sample size required is 292.

If the prevalence is low, 'deff' for cluster sampling is usually close to unity. The sample size calculated is still relatively applicable even if cluster sampling is employed because of the small prevalence.

If the estimated prevalence is close to 50%, a delta of 25% is too large. It would be better to reduce this to ±5% or ±10% of the prevalence. If cluster sampling is employed under such a condition, the value of 'deff' is usually greater than one.

For example, in standard 30-cluster sampling for assessment of immunization coverage where the prevalence is estimated to be near 80%, 'deff' should be around 2. The population size in this case is usually large and a 99% confidence limit is required instead of 95%. In this case, the suggested calculation would be:

```
> n.for.survey(p =.8, delta =.1, deff=2, alpha=.01)

Sample size for survey.
Assumptions:
  Proportion       = 0.8
  Confidence limit = 99 %
  Delta            = 0.1 from the estimate.
  Design effect    = 2

  Sample size      = 212
```

With this total sample size of 212 and 30 clusters, the average size per cluster would be 212/30 = 7 subjects. This sample size could be used for a standard survey to assess immunization coverage in developing countries.

Comparison of two proportions

In epidemiological studies, comparison of two proportions is quite common.

As the name indicates the function *`n.for.2p`* is written for this purpose. As before, the necessary arguments to this function can be examined as follows:

```
> args(n.for.2p)
function(p1, p2, alpha = 0.05, power = 0.8, ratio=1)
```

In a case-control study, the proportion (p1) of subjects exposed to a risk factor among the cases (diseased group) is compared against the proportion (p2) of subjects exposed among the controls (non-diseased group).

In a cohort study, the probability (p1) of getting a disease among the exposed group is compared to the probability (p2) among the non-exposed group.

In a randomised controlled trial, the probability (p1) of getting cured (or improving) among subjects given a new treatment is compared with the probability (p2) of getting cured (or improving) among subjects given the old treatment.

The argument alpha is the probability of committing a Type I error. If the two groups actually have the same proportion at the population level (the null hypothesis is true), with the sample size from this calculation, there will be a chance of 'alpha' that the null hypothesis will be rejected. In other words, the difference in the two samples would be erroneously decided as statistically significant. As before, it is common practice to set the alpha value at 0.05.

The power of a study is the probability of rejecting the null hypothesis when it is false. In this situation it is the probability of detecting a statistically significant difference of proportions in the population, which is in fact as large as that in the sample. It is quite acceptable to have the power level set at 80%. The type II error is simply 1-power, and is the probability of not rejecting the null hypothesis when it is false. Scientists usually allow a larger probability for a type II error than for a type I error. Rejecting a new treatment that is actually better than the old one may probably be considered less serious than replacing the old treatment with a new one which is in fact not better.

The 'ratio' refers to the ratio of the number of subjects in sample 1 to the number of subjects in sample 2. For these three types of studies, the most efficient sample size (smallest size of total sample that can test the hypothesis) is achieved when the ratio between the two stratified groups is 1:1. For example, if the collection of data per subject is fixed, comparing two groups of treatment each of 50 subjects is much better than comparing 5 subjects in one group against 95 subjects in the other. In certain conditions, such as when a very rare disease is under investigation, it might be quicker to finish the study with more than one control per case. In addition, in a cross-sectional study, the status of a subject on exposure and outcome is not known from the beginning; the sample is non-contrived. The ratio cannot be set at 1:1 but will totally depend on the setting. Under these conditions where the ratios are not 1:1, the value of the ratio must be specified in the calculation.

For example, if a risk was determined to be as common as 50% among the diseased group and 20% among the control group, the minimum sample size required to detect this difference for a case control study can be calculated by:

```
> n.for.2p(p1=0.5, p2=0.2)

Estimation of sample size for testing Ho: p1==p2
Assumptions:

     alpha = 0.05
     power = 0.8
        p1 = 0.5
        p2 = 0.2
     n2/n1 = 1

Estimated required sample size:

        n1 = 45
        n2 = 45
   n1 + n2 = 90
```

The use of this function is not complicated, as only 'p1' and 'p2' are needed to be input. The other arguments will be set to the default values automatically. In conclusion, only 45 cases and 45 controls are needed to test the hypothesis of no association. If the disease is rare, say only 10 cases per year, and the researcher wanted to complete the study early, he/she may increase the case:control ratio to 1:4

```
> n.for.2p(p1=0.5, p2=0.2, ratio=4)

Estimation of sample size for testing Ho: p1==p2
Assumptions:

     alpha = 0.05
     power = 0.8
        p1 = 0.5
        p2 = 0.2
     n2/n1 = 4

Estimated required sample size:

        n1 = 27
        n2 = 108
   n1 + n2 = 135
```

Note that the ratio is n2/n1. This study can be finished in less than 3 years instead of originally 4.5 years. Increasing the ratio above this has only a small effect on reduction of number of cases but a remarkably high effect on increasing the number of controls. For example, a ratio of 1 case per 9 controls will reduce the required sample size to 23 cases (4 cases reduced) but increase the number of controls required to 207 (an increase of nearly 100).

An increase in power from 0.8 to 0.9 also increases the requirement for the sample size considerably. Fixing the ratio at 1:1

```
> n.for.2p(p1=0.5, p2=0.2, power=0.9)
```

The output is omitted, however 58 cases and 58 controls are required (an increase of 29% of the sample size required on both arms).

Relationship between p1, p2 and odds ratio in a case control study

To be consistent with the above agreement, the odds ratio would be the ratio of the two odds of exposure: p1/(1-p1) / {p2/(1-p2)}.

```
> .5/(1-.5)/(.2/(1-.2))
[1] 4
```

Setting up 'p1' and 'p2' for calculation of sample size for a case control study is straightforward. However, in some instances, there may be a demand to compute the sample size based on proportion of exposed in the general population (which is equal to the proportion among the controls due to the rarity of the disease) and the odds ratio. In other words, 'p2' and odds ratio are given. It remains necessary then to find 'p1'.

For example, if the proportion of exposures among the population (p2) is equal to 30%, and the odds ratio is 2, the proportion of exposures among the cases (p1) and the required sample size can be calculated as follows:

```
> p2 <- 0.3
> or <- 2
> odds2 <- p2/(1-p2)
> odds1 <- or*odds2
> p1 <- odds1/(1+odds1);  p1
 [1] 0.4615385
> n.for.2p(p1,p2)

Estimation of sample size for testing Ho: p1==p2
Assumptions:

     alpha = 0.05
     power = 0.8
        p1 = 0.4615385
        p2 = 0.3
     n2/n1 = 1

Estimated required sample size:
        n1 = 153
        n2 = 153
   n1 + n2 = 306
```

The required sample size is larger than in the preceding example because the odds ratio to be detected is closer to unity. In other words, the level of difference to be detected is smaller.

Cohort study and randomised controlled trial

Given that 'p1' and 'p2' are the respective success rates among the two treatment or exposure groups, the calculation is fairly straightforward.

In fact, whether the calculation is based on the success rate or the failure rate, the answer is the same. For example, if treatment A gives a success rate of 90% and treatment B gives a success rate of 80%, we may also say that treatment A and B have failure rates of 10% and 20% respectively. The calculation of sample sizes in both cases would yield the same result.

```
> n.for.2p(p1=0.9, p2=0.8)

===== details omitted =========
        n1 = 219
        n2 = 219
   n1 + n2 = 438

> n.for.2p(p1=.1, p2=.2)

===== details omitted =========
        n1 = 219
        n2 = 219
   n1 + n2 = 438
```

Cross-sectional study: testing a hypothesis

A cross-sectional survey serves two purposes, firstly to document the prevalence of a condition (either a disease or an exposure condition or both), secondly to test the association between the exposure and the outcome. This sample size for hypothesis testing is different from that for the descriptive purpose (which has been fully discussed above).

Calculation of the sample size for the second component (hypothesis testing) of the cross-sectional study should be based on the *n.for.2p* function. Similar to the cohort study and the randomised controlled trial, the proportions, 'p1' and 'p2', should be orientated toward the outcome in each exposure group where 'p1' is equal to the proportion of positive outcomes among the exposed group, and 'p2' is equal to the proportion of positive outcomes among the non-exposed group.

On the other hand, the value of the 'ratio' is the ratio between the exposed and non-exposed groups, which must be estimated from the prevalence of the exposure.

For example, in a survey, the prevalence of exposure might be estimated to be 20%, the probabilities of getting a disease are 20% and 5% among the exposed and the non-exposed population.

With the prevalence of exposure being 20% the ratio n2:n1 would be 0.8/0.2 = 4.

```
> n.for.2p(p1=0.2, p2=0.05, ratio=4)
Estimation of sample size for testing Ho: p1==p2
Assumptions:

     alpha = 0.05
     power = 0.8
        p1 = 0.2
        p2 = 0.05
     n2/n1 = 4

Estimated required sample size:
        n1 = 48
        n2 = 192
   n1 + n2 = 240
```

The total sample size for this cross-sectional survey to test the hypothesis is 240 subjects. This will include 48 exposed and 192 non-exposed persons.

This required sample size should be checked for adequacy of the other objective, i.e. to describe the prevalence of exposure, which is estimated to be 20%.

```
> n.for.survey(p=0.2)

Sample size for survey.
Assumptions:
  Proportion       = 0.2
  Confidence limit = 95 %
  Delta            = 0.1 from the estimate.

  Sample size      = 61
```

The required sample size of the descriptive study is smaller than that for hypothesis testing. Thus, the latter (of 240 subjects) should be adopted.

Comparison of two means

In epidemiology, comparison of two means is not as common as that of two proportions. This is mainly because a clinical or public health decision is mainly based on a hard-evidenced dichotomous outcome and less on the level of difference of the mean values. However, there are also a lot of important health outcomes that are measured on a continuous scale, the difference of means of which can be of important social concern. Examples of continuous outcomes include intelligence quotient, pain scores and quality of life.

Two sample means usually have two different standard deviations. Thus the function for this calculation requires a few more arguments.

```
> args(n.for.2means)
function(mu1, mu2, sd1, sd2, ratio=1, alpha=0.05, power=0.8)
```

Intuitively, the notation is straightforward. There are four compulsory arguments that a user must supply to the function, namely the two means and their corresponding standard deviations.

Note:

Readers may be aware now that function arguments that include an equals sign followed by a value are optional. The value to the right of the sign is the default value used by the function when the argument is omitted. Arguments that do not include an equals sign are, however, compulsory. If omitted, an error is generated.

As an example, suppose a new therapeutic agent is expected to reduce the mean pain score from 0.8 to 0.6 in a group of subjects and the expected corresponding standard deviations are 0.2 and 0.25. To calculate the required sample size, type the following command:

```
> n.for.2means(mu1=0.8, mu2=0.6, sd1=0.2, sd2=0.25)

Estimation of sample size for testing Ho: mu1==mu2
Assumptions:
     alpha = 0.05
     power = 0.8
       mu1 = 0.8
       mu2 = 0.6
       sd1 = 0.2
       sd2 = 0.25

Estimated required sample size:
        n1 = 21
        n2 = 21
   n1 + n2 = 42
```

This anaesthesiological experiment would require 21 subjects in each group.

In fact, the mathematical formula for the calculation of the sample size does not require the exact values of 'mu1' and 'mu2'. If the difference in means and the standard deviations are fixed, changing the two means will have no effect on the calculated sample size. Thus the same results are obtained from the following command (output omitted).

```
> n.for.2means(mu1=0.4, mu2=0.2, sd1=0.2, sd2=0.25)
```

Lot quality assurance sampling

Lot quality assurance sampling (LQAS) was initially applied to manufacturing processes. A company takes a sample in order to check whether the lot of product is ready to be shipped. If the percentage of defectives is estimated to be higher than a certain level, the lot is rejected. Otherwise, the whole lot is shipped to the market.

The difference between LQAS and other sampling methods is that LQAS does not estimate the exact percentage of defectives. It only checks whether the acceptable level is exceeded. The required sample size for this process is smaller than that for estimation of a prevalence or proportion. Thus, the costs of checking can be decreased very considerably if the quality analysis of individual components is high.

Health systems adopt LQAS mainly for surveillance of proportion of problems. For example, in the process of quality assurance of anti-TB drugs in southern Thailand, content assays and dissolution tests of the drug are rather expensive. The LQAS method was employed to calculate the minimal sample size that is still sufficient to test whether the quality is acceptable.

Suppose a highest acceptable proportion of defective specimens is set at 1 percent. If the study suggests that the actual proportion is at this level or less, then the lot is accepted. Otherwise, the whole lot will be rejected. The actual proportion (whether it be higher or lower than this acceptable level) is not important. If the sample size is too small, say 20, then even if all randomly selected specimens were accepted, it would still not be certain that less than 1% of the whole lot was defective. If the sample size is too big, say 1000, then even if the percent defective is within the reasonable level, you have wasted all those specimens that were tested. This large sample size is excessive.

With an optimal sample size, should any of the randomly selected specimens be defective, the acceptable proportion of the whole lot would be expected to be exceeded. One of the easiest ways to understand this is to look at the computation results.

```
> n.for.lqas(p=0.01)

     Lot quality assurance sampling

                             Method = Normal approximation
                    Population size = 10000
  Maximum defective sample accepted = 0
     Probability of defect accepted = 0.01
                              Alpha = 0.05
               Sample size required = 262
```

From this computation, the threshold for the defective proportion (p) is set at 1%. The final sample size is 262. The lot size is assumed to be 10,000 by default. The maximum defective sample accepted is 0 (again the default). This means that if any of the 262 specimens is defective, the proportion of 1% is considered to be exceeded and the lot is rejected. With this sample size, the researcher would take a random sample of 262 specimens and examine each one. If all of the specimens pass the tests, the remaining lot of 10,000-262 = 9,738 specimens can be marketed. Otherwise, all 10,000 will be rejected.

There are a few parameters controlling the sample size here. Alpha (the type I error rate) is usually set at 5%. This means that if the null hypothesis (the defective percentage is less than 1%) is true, there is a 5% chance that there would be at least one defective specimen among the whole sample of 262. If alpha is set to a stricter criterion, say 2.5%, the sample size will increase.

The threshold proportion for a sample being accepted varies inversely with the sample size. If the threshold is increased, say to 3%, the required sample size would be reduced (only 87 would be needed).

The maximum defective sample accepted is set at 0 by default in order to minimize the sample size. In theory, this can be any number. However, the larger the number is, the larger the required sample size.

Power determination for comparison of two proportions

Sometimes a reader may come across a study that reports no significant difference between two groups. One may doubt whether the study had enough power to detect the significant difference if a clinically significant difference existed at the population level. Consider a trial with 105 subjects on one treatment arm consisting of 35 failures versus 50 subjects on a placebo with 20 failures. To set up this hypothetical data table, you may type the following commands:

```
> table1 <- c(35,70,20,30)
> dim(table1) <- c(2,2)
> table1 <- as.table(table1)
> cc(cctable=table1)
        A  B Total
A      35 20    55
B      70 30   100
Total 105 50   155
OR =  0.751
95% CI = 0.354 1.606
Chi-squared = 0.658 ,  1 d.f. , P value = 0.417
Fisher's exact test (2-sided) P value = 0.474
```

The odds ratio of 0.75 has a rather wide confidence interval. It might be of interest to know the power of the sample size for this particular study if the true odds ratio is in fact 0.5 and the failure rate among the placebo group is the same.

```
> odds.placebo <- 20/30
> odds.treat <- .5 * odds.placebo
> p.placebo <- 20/50
> p.treat <- odds.treat/(1+odds.treat)
> power.for.2p(p1=p.treat, p2=p.placebo, n1=105, n2=50)
     alpha = 0.05
        p1 = 0.25
        p2 = 0.4
        n1 = 105
        n2 = 50
     power = 0.4082
```

The sample size used in this study only had a 40% chance of finding a significant difference given that the treatment had an odds ratio of 0.5. The study was therefore inconclusive.

Note that the power depends on the size of difference to be detected. To obtain statistical significance for a large difference would require a smaller sample size than that for detecting a small difference if the power was kept the same.

Power for comparison of two means

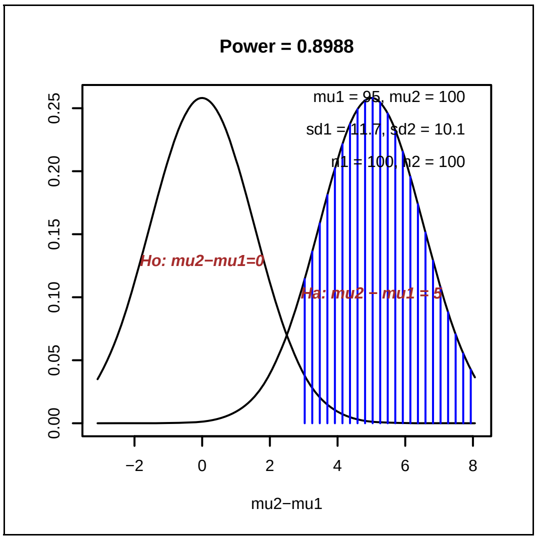
Suppose a study reports that in a randomised controlled trial a micro-nutrient is given to 100 pupils and a placebo to another randomly selected 100. By the end of the year, the mean ± standard deviation of the IQ scores in the two respective groups is 98 ± 10.1 and 95 ± 11.7.

What is the power to determine an improvement of 5 units (new IQ = 100) if the parameters in the placebo groups and the standard deviation of the treatment group are not changed?

Let group 1 represent the pupils on the placebo and group 2 be the pupils receiving the new treatment. The command to calculate the power is:

```
> power.for.2means(mu1=95, mu2=100, sd1=11.7, sd2=10.1,
  n1=100, n2=100)
     alpha = 0.05
       mu1 = 95
       mu2 = 100
        n1 = 100
        n2 = 100
       sd1 = 11.7
       sd2 = 10.1
     power = 0.8988
```

With this relatively large sample size, the power to detect a difference of 5 points of IQ under these assumptions is approximately 90%.



Exercises

Problem 1.

Calculate the maximum sample size required to estimate the prevalence of respiratory tract infection, with a precision of 5%, in a target population consisting of children aged 1-5 years in a particular region of a developing country.

Problem 2.

A case-control study is carried out to determine the efficacy of a vaccine for the prevention of childhood tuberulosis with a placebo. Assume that 50% of the controls are not vaccinated. If the number of cases and controls are equal, what sample size is needed to detect, with 80% power and 5% type I error, an odds ratio of at least 2 in the target population?

Problem 3.

A randomised trial is to be conducted comparing two new treatments aimed at increasing the weights of malnourished children with a control group. The minimal worthwhile benefit is an increase in mean weight of 2.5kg, and the standard deviations of weight changes are beleived to be 3.5kg.

What are the required sample sizes, assuming that the control group is twice as large as each of the two treatment groups and an 80% power is required for each comparison?

Chapter 25: Documentation

Data can be analysed interactively as shown in the previous chapters or in a batch mode as shown in this chapter.

Starting with interactive analysis

In the interactive mode, the analyst types commands directly into the console and, if there are no errors, obtains the output specific to that command. This is very useful when he/she starts to learn the software for the first time. Typing and reading commands from the console is the most natural learning process. This learning phase of typing commands one at a time often results in several mistakes, either syntactically or otherwise. The most common type of mistake is syntax error or violation of the rules imposed by the software. Examples include unbalanced brackets, unbalanced quotes and omission of delimiters (such as commas). These mistakes however are easy to correct. The user can simply press the up arrow key to retrieve the previous command and make the appropriate corrections.

At the initial phase of the analysis, the analyst needs to get acquainted with the dataset and the variables. This phase is often called 'Exploratory data analysis', which is mainly carried out interactively. Under Epicalc, this can be done with the following steps:

Starting with clearing the memory

```
> zap()
```

Loading the necessary libraries for a particular purpose of the analysis, such as `library(survival)` for analyzing survival data, `library(nlme)` and `library(MASS)` for multi-level modelling.

Reading in data files

If the dataset is in EpiInfo format (file extension = ".rec"), Stata (".dta"), SPSS (".sav"), or comma separated values (".csv") then it would be convenient to read in the data file with the command *`use`*`("filename")` from the Epicalc library.

If the data is in another format, check whether the first line is a header (variable names) and check the type of the variable separator. The appropriate command to read in the dataset is `read.table` from the **base** library.

For other data file formats, type

```
help.start()
```

Choose 'packages' and then 'foreign'.

Explore the class and description of variables using *`des`*`()`. Quickly explore summary statistics of the variables using *`summ`*`()`.

Explore each variable one at a time using the command *`summ`*`(varname)`. Pay attention to the minimum, maximum and look at the graph to see a detailed distribution. Explore categorical variables using *`codebook`*`()` and *`tab1`*`(varname)`.

Save the commands that have been typed using `savehistory("filename")`. The saved file should have a ".r" or ".rhistory" extension. This file stores all the commands that have been typed in. These commands will be used for further analysis.

Note that 'varname' and 'filename' in the above list should be replaced with the appropriate variable name and file name. Commands typed in during the interactive modes often contain mistakes. Since these commands will be reused in the future, they should be 'cleaned up' using an appropriate text editor. The next step is to open the saved file with a text editor. Crimson Editor and Tinn-R are recommended for this purpose.

Crimson Editor

There are many good text editors available for editing a command file. A good one should be able to show line numbers and matching brackets. The Notepad program that comes with Windows does not have these features and is thus not suitable for working with a long command file. The current recommended programs are Crimson Editor and Tinn-R, which are both public domain software.

Use Windows Explorer to create a new text file. By default, Windows will offer to name the file, say 'New Text Document.txt'. Do not accept this name. Instead choose a name appropriate to the purpose of the file, such as 'Chapter1' or 'HIV' and make sure you include the '.R' or '.r' extension. Double click this new file. If your computer's file associations have been successfully set up, your computer should open it with either Crimson Editor or Tinn-R. If not, right click and choose 'Open with' then choose Crimson Editor (cedt.exe) or Tinn-R (Tinn-R.exe).

The following section is specific for Crimson Editor only. You may use this newly created file to customise Crimson Editor menus and file preferences.

Choose 'View', 'Tool bars/Views'. Check 'Tool bar', 'MDI file tabs' and 'Status bar'. If you want to know what work they do, just uncheck them one by one.

Note that Crimson Editor can have multiple files opened simultaneously. Any file that has been changed but not yet saved will have a red dot in its MDI File tab. This turns green once the file has been saved.

From the menu bar select 'Document', 'Syntax types'. See if **R** is in the list of known file types. If not, select 'Customize...' at the very bottom of the list. The 'Preference' dialog box will appear with 'Syntax Type' highlighted under the 'File' option. In the list of Syntax Types, scroll down until you see the first '-Empty-' position and select it with the mouse. Position the cursor in the 'Description' text box and type R. Next to 'Lang Spec', type 'R.spc', and for 'Keywords' type 'R.key'. Finally Click 'OK'. Language specification and key words for the **R** program will be available for any file opened with Crimson Editor. But the **R** command file is still not automatically associated with Crimson Editor yet. The user needs to activate this by clicking 'Document', 'Syntax types' and selecting 'R' from the list.

Finally, for the line number, Click 'Tool's from the menu bar, then 'Preferences...'. In the Preferences box, highlight 'Visual'. Check 'Show line numbers', 'Highlight active line' and 'Highlight matching pairs'.

Tinn-R

The advantage of using Tinn-R over Crimson Editor is it's ability to interface or interact with **R** itself. Users can type the commands into the Tinn-R editor and send them to the **R** console line by line, in blocks of lines, or even the whole command file. Tinn-R has many other nice features similar to Crimson Editor that make working with **R** easier and more convenient.

Viewing line numbers is strongly recommended. This can be set under the View menu. Those who like to use the function keys instead of the mouse can set the 'hotkeys' of **R**, under the R menu. The authors preference is to set F2 for sending a single line, F4 for sending the selected block, F5 for sending the current whole command file without prior saving and F6 for saving the file and sending as 'source'. The function key F3 is preserved for Searching (and find again).

Editing a command file

A command file can be very simple or very complicated, depending on the nature of the work. For a command file with only a few simple steps, the level of complication is not high. Editing is not too difficult. The editing tasks include the following steps:

Open the saved history file using either Crimson Editor or Tinn-R. Correct any lines that have incorrect syntax. The last line 'savehistory("filename.r")' should be removed because it is not needed in the batch mode.

Correct the typing mistakes by deleting lines of erroneous commands.

Remove any duplicate commands.

Check the structure of the commands. Make sure it includes proper order of key commands as suggested above (with *zap*, *use*, etc) .

If you use Crimson Editor, you may copy blocks of commands and paste them into the **R** console. If you use Tinn-R, you can simply highlight the commands that you want to send to **R** and using the mouse, click on the “send” icon (or press the hot-key) to perform the operation. Copying and pasting has the advantage of seeing different colours of commands (red) and output (blue) on the **R** console. However, any mistake or error in the middle of a large block of commands may escape notice. If the block of commands contains an error, then saving and sending commands as source will stop at the line containing the first error. For example,

```
Error in parse(file, n = -1, NULL, "?") : syntax error at
3: library(nlme
4: use("Orthodont.dta")
```

The report on syntax errors usually includes the line numbers of the (first) error. In the above example, the error occurs at line 3 (missing closing bracket). Return to the command file and make the appropriate correction, followed by saving the file.

Even when all syntax errors have been removed, there may remain other types of command errors, such as typing mistakes in commands, objects not found or files not being able to be opened. In these situations, the console will show the results in the console up to the error line. However the line number will not be given. Switch back to the command file and correct the error then return to the **R** console and re-run the command

```
> source("filename.r", echo=TRUE)
```

The lines that need to be skipped by **R**, such as author's comments or commands that the analyst want to skip for the time being can begin with #. It is highly recommended that comments be included throughout the command file to enable other readers to follow easily.

The amount of commands typed into the command file should be optimal. It is a good practice to have the newly added command lines containing one set of related actions. For example, commands to create a new categorical variable from a continuous variable and to check the distribution of this new variable (using `tab1(newvar)`) should be kept together. Executing the command file at this stage will allow the analyst to check this part of results instantly. Once the new variable is assured, the line `tab1(newvar)` may not be necessary and can be subsequently deleted or skipped by placing a '#' before it.

One of **R**'s advantages is in its graphing capabilities. Graphing however can involve many steps and may require the addition of extra graphical parameters. It is a good idea to start with a simple graph in a command. Other parameters such as 'pch' (point character), 'lty' (line type), 'xlab' (X-axis label), 'col' (colour) etc, can be added in the next round of command editing. Eventually, a good graph may need several lines of commands to produce it.

Breaking in the middle of the command file

Since there can be several commands in the command file executed continuously, the results coming out on the console can be too much to store in the console buffer or too much to read. A graph created from a command line will also be overwritten by a subsequent graph. It is often necessary to break or interrupt the command file to see the details or graph at some point. To do so, insert a line where the break is required. Type a single meaningless word such as 'xxx' on that line. Save and run the file. When the command file is executed to this point, **R** does not know what to do and thus stops with an error message. The output just before the 'xxx' can be fully explored and any graph that is currently displayed can be saved.

The command at the **R** console `source("filename.r")` to run the command file can be easily repeated by pressing the up arrow key and then <Enter>. Changing the breaking point of 'xxx' from one place to another in the command file followed by saving it and resourcing the file at the **R** console is a standard method of making good use of an existing command file.

Executing only a section of a command file

The above method, once established, ensures that the command file has no syntax errors and the system works well up to the point of 'xxx'. The method however may add too much time if some of the data file and/or command file are large or the computation process is CPU intensive. Sometimes, the analyst may want to by-pass these preceding sessions to get quick results from the section in the later part of the command file. This can be done if and only if the preceding sections are not the requirement of the section needed. For example, a section starting with `zap()` or `rm(list=ls())` will erase almost all objects and attachments. Any preceding sections could possibly be bypassed without much a problem.

Bypassing several lines in the command file

If a few lines need to be bypassed but not erased, the easiest way is too put # in front. However, if there are too many lines to do so and all the lines are contiguous, one can bypass them using the '`if(){...}`' control construct. If the expression in the first (round) bracket is FALSE, all the commands inside the curly brackets {} will be bypassed. Thus to bypass a large section, one simply inserts one line with the command:

```
if(FALSE){
```

just before the to-be-bypassed section, and one line with a closing curly bracket at the end of that section. The whole section contained by the curly brackets will be skipped.

The main problem with this method is finding and removing the matching curly brackets when the bypass is no longer required and the command file has been unused for a long time. Crimson Editor and Tinn-R have a highlighting facility for matching brackets but the opening and the closing ones sought may be very far apart with several other curly brackets nested inside. To prevent this confusion, several blank lines should be inserted before the command line 'if(FALSE){' and after the matching closing bracket. These blank lines will make the skipped section easily visualised.

Saving the output text

There are a number of methods to save the output text.

The simplest way is to highlight the area of text with the mouse and copy it to the clipboard before pasting to a destination area such as a part of document text.

An alternative method is to use the `sink(file = "myFile.txt")` command to divert all the subsequent output text to a file, named "**myFile.txt**". See 'help(sink)' for more details about the usage of this function. To return to interactive mode, i.e. to stop diverting output to the file, issue the command `sink()`. The use of `sink` may be incorporated into the command file or carried out manually.

A complication of using `sink` arises when there is an error in subsequent commands. Since the results are diverted to a file, not to the screen, the use will not recognize the error and the process will stop in the middle of confusion. If this happens, the solution is to type `sink()` at the console. This will return the route back to the screen. The errors are can then be investigated in the output file. To prevent this, the command `sink` should used only when all the commands have been tested to be error free, for example no 'xxx' or other garbage allowed. The command `sink(file="myFile.txt")` can then be placed at the beginning of the command file and `sink()` placed at the end of the file. Then submit the command file to **R** with the command `source("command file")`.

Perhaps the simplest and best method to save the text output is to click 'File' at the menu bar and choose 'Save to File...'. This will save all output currently in the console to a text file. The default destination file is "**lastsave.txt**" but this can easily be changed.

Note:

This last method will not save output if the 'clear console' command has been issued. In addition, there is a limit to the number of lines that can be saved. **R** limits the console window to the last 5,000 or so lines that can be saved. Therefore use this method only if your output is not very long.

Saving a graph

Routing saving of a graph to a file is simpler than routing the output text. Copying a graph to the clipboard and then pasting it to a program such as a word document or a PowerPoint presentation slide is simple. Click at the graph window and choose 'File' from the menu bar and 'Copy to the clipboard. Choose as a Bitmap or Metafile if the destination software can accept this format. A Metafile is slightly smaller in size and has a sharper line. The Bitmap format may not have a sharp picture when the size is enlarged. Alternatively, the graph can be saved in various other formats, such as JPEG, postscript or PDF.

To save a graph when commands are run from a source file, simply type 'xxx' after the graphing command to halt further execution of commands. Then copy or save the graph as mentioned above.

Alternatively, instead of showing the graph on the screen, the graph can be routed to a file by issuing one of the following graphics device commands:

```
bmp("filename.bmp")
jpeg("filename.jpg")
png("filename.jpg")
win.metafile("filename.wmf")
pdf("filename.pdf")
```

Each of these commands sets up the graphics device and must be followed by a command that creates the actual graph. When the commands that create the graph are executed, it is important that the device is turned off in order to write the graph contents to the file and reroute future graphical output to the screen.

```
dev.off()
```

This rerouting method is useful because the whole process of the command file need not be interrupted in the middle by the method mentioned in the preceding paragraph.

The concept of turning the graphics device off after creating the graph is similar to using the `sink` command, which requires a final `sink()` to save and close the file. The commands below create a summary graph of the variable 'age' from the **`Outbreak`** dataset in Epicalc. The graph is routed to a file called "**graph1.jpg**".

```
> zap()
> data(Outbreak)
> use(Outbreak)
> jpeg("graph1.jpg")
> summ(age)
> dev.off()
```

The re-routing process can be done either interactively or inside a command file if there are no mistakes inside the graphics commands.

Chapter 26: Strategies of Handling Large Datasets

The datasets given in the Epicalc package and used in this book are relatively small, both in number of records and the number of variables. In real life, a data analyst often faces over 50 variables and several thousand records. The requirements for such analytical processing include a large amount of computing memory, fast CPU, large hard disk space, and efficient data handling strategies. Without these requirements, data analysis may take too long or may not even be possible.

Clearing R memory

R can handle many objects in one session. If the amount of memory is limited, it is a good practice to clear all unnecessary objects from the working environment and detach from all unnecessary data frames. Therefore, it is advisable to start any new project with the following two commands.

```
> zap()
> detachAllData()
```

Simulating a large dataset

Instead of using an existing large dataset, let's create a data frame containing 30,000 records with 161 variables. The `rnorm` function is used to generate the random numbers from a standard normal distribution.

```
> data1 <- rnorm(30000*160)
> dim(data1) <- c(30000, 160)
> data1 <- data.frame(id=1:30000, data1)
```

The first variable is called 'id'. The naming of the remaining 160 variables can be achieved using two nested `for` loops and the built-in **R** constant '`letters`', which consists of the lower-case letters of the English alphabet. The outer loop generates the first character of the variable names (a – h). The inner loop then pastes the numbers 1 – 20 to these letters, separating the letters and numbers with a full stop.

```
> namesVar <- NULL
> for (i in letters[1:8])
  {
    for(j in 1:20){
      namesVar <- c(namesVar, paste(i, j, sep="."))
    }
  }
> names(data1)[2:161] <- namesVar
```

Then give a variable description to each variable, using the `attr` function. This process should only take a few seconds, depending on the speed of your computer.

```
> attr(data1, "var.labels")[1] <- "ID number"
> for(i in 2:161){
   attr(data1, "var.labels")[i] <- paste("Variable No.", i)
  }
> use(data1)
```

Describing a subset of variables

After entering commands at the **R** console, large output will usually scroll off the screen, making viewing awkward. To show a subset of the variables in the data frame, specify the 'select' argument in the *`des`* function.

```
> des(select=1:20)
```

Only the first 10 variables, their class and description will be shown. Then we move to see the next twenty.

```
> des(select=21:40)
```

... and so forth. Glancing at about 20 variables at a time will allow users to see the variable descriptions more carefully, without having to scroll up and down the screen.

If one wants to see only the variables names that start with "a", type:

```
> des(select="a*")
```

In this case, there are 20 of them.

To look at the variable descriptions of variables starting with "a." followed by only one character, type:

```
> des(select="a.?")
```

Keeping only a subsample

Working with such a large data set can be time-consuming. When testing **R** commands it may be better to just keep a subset of records, thus reducing the time involved. When you are satisfied that the commands work correctly, then you can apply it to the whole dataset. The Epicalc function *`keepData`* can be used to select a subset of records from the whole data frame.

```
> keepData(sample=300)
```

The data frame **`.data`** will be changed from having 30,000 to having only 300 records with the same number and description of variables, as can be seen from

```
> des(.data)
```

Note that the first few lines read:

```
 (subset)
No. of observations =300
    Variable      Class           Description
1   id            integer         ID number
2   a.1           numeric         Variable No. 2
========= lines omitted=========================
```

which suggests that **`.data`** is just a subset of the original one.

If one wants to use the original data frame, simply type

```
> use(data1)
```

An alternative to specifying the number of records to randomly keep is to specify a percentage of the original records. This is done by specifying a number between 0 and 1 for the 'sample' argument.

```
> keepData(sample=0.01)
```

The above command would again keep only 300 of the original number of records. The criteria for keeping records can also be specified using the 'subset' argument:

```
> keepData(subset=a.1 < 0)
```

You will see a reduction of the total records, but not the variables.

```
> des()
```

The reduction is about a half since the variable 'a.1' was generated from a standard normal distribution, which has a mean of 0 and is symmetric about this mean.

This method of selecting subsets of records can be applied to a real data frame, such as keeping the records of only one sex or a certain age group.

Data exclusion

The *keepData* function can also be used to exclude variables. Return to the original data frame and exclude the variables between 'a.1' and 'g.20'.

```
> use(data1)
> keepData(exclude = a.1:g.20)
> des()
```

Variables from 'a.1' to 'g .20' have been excluded but note that the number of records remains the same.

To exclude the last 10 items of each section, the wildcard feature of Epicalc can be exploited.

```
> use(data1)
> keepData(exclude = "????")
> des()
```

All the variables with a name of length four characters have been removed.

As mentioned before, if the size of the data frame is large, the analyst can choose one or more of the above strategies to reduce the size. Further analysis can then be carried out more quickly. If all the commands are documented in a file as suggested by the previous chapter, and the commands are well organized, the first few lines of the file can then be edited to use the full original data frame in the final analysis.

Chapter 27 Table Stacking for a Manuscript

Readers of this book may wonder why simple statistical tests such as the t-test, chi-squared test and non-parametric tests are rarely mentioned or explained in detail. They are often used in the initial comparison of groups, which is commonly presented as the first table in most epidemiological manuscripts. All these statistical tests can be produced by one single Epicalc command, `tableStack`.

In chapter 23, this command is extensively used in parallel with the commands `alpha` and `alphaBest` to display the distribution of each variable. An additional (and also more important) goal is to compute the mean and total scores with the items correctly reversed where necessary.

In this chapter, the same function is also extensively used but with the 'by' argument included. The results of this can go directly into the manuscript.

Concept of 'tableStack'

Epidemiological and clinical manuscripts often have objectives of testing certain hypothesis in human subjects. These subjects are usually grouped by type of exposure (in a cohort or an interventional study) or outcome (in a case control study) of interest. This grouping variable is initially analysed against baseline characteristics in the first table of the manuscript and against the variables of hypothesis testing in the second table. The orientation of the tables usually has the group variable as the column and other variables as the rows.

In practice, if the row variable is a factor, then one can either use the `table` function from the **base** library or `tabpct` from Epicalc, which will both show a cross-tabulation of the variables. This is then subject to statistical testing using either a chi-squared test or Fisher's exact test.

If the row variable is on a continuous scale, the required table could be obtained by the `tapply` or `aggregate` functions in the **base** and **stats** packages of **R**, respectively, which give one statistic of each subgroup at a time or *`aggregate.numeric`* from the Epicalc package, which gives multiple statistics of the subgroups. If the data are normally distributed, means and standard deviations are the two commonly displayed statistics. For data with skewed or non-normal distributions, the median and inter-quartile range (25th and 75th percentiles) are often used. For normally distributed data the t-test, for testing between two groups, and one-way anova, for testing than two groups, are used. For non-normal data, non-parametric tests are favoured, ie. the Wilcoxon rank sum test for 2 groups and the Kruskal-Wallis test for more than 2 groups.

In doing so, the analyst has to go through various steps of exploring the distributions, computing different statistics for the subgroups and then copying the results into the manuscript, usually with some time-consuming formatting required. This labourious work is easily accomplished by the Epicalc function *`tableStack`*, which creates and stacks several tables with the appropriate statistics together into one convenient table.

Example

All datasets with at least one factor variable can be used for trial. Let's start with the dataset **`Familydata`**, a small dataset previously explored in chapter 4.

```
> zap
> data(Familydata)
> use(Familydata)
> des()

Anthropometric and financial data of a hypothetical family
No. of observations = 11
  Variable      Class           Description
1 code          character
2 age           integer         Age(yr)
3 ht            integer         Ht(cm.)
4 wt            integer         Wt(kg.)
5 money         integer         Pocket money(B.)
6 sex           factor
```

The data contains only one factor variable, 'sex'. Now we create a summary table of all variables by each level of sex, in a nice stacked format, with the appropriate statistical test shown.

```
> tableStack(vars=2:5, by=sex)
               F              M            Test stat.        P value
Age(yr)                                    t (9 df): t = 0.5   0.627
  mean(SD)     42.9(24.3)     50.8(26.6)

Ht(cm.)                                    Rank sum: W = 0.5   0.014
  median(IQR)  155(150.5,159) 168.5(166,170.5)

Wt(kg.)                                    Rank sum: W = 3     0.047
  median(IQR)   51(50.5,54)    65.5(61,68)

Pocket money(B.)                           t (9 df): t = 1.33  0.218
  mean(SD)      586.4(656.1)   1787.5(2326.1)
```

The numeric argument of 'vars' can also be replaced with the variable names.

```
> tableStack(age:money, by=sex)
```

The output table consists of four variables, which come from the second to the fifth (vars=2:5) in the dataset. Age is determined to be normally distributed, thus a t-test is conducted to test for a difference between the mean ages of males and females. The test statistic is small (t=0.5), with 9 degrees of freedom and non-significant P value.

Height and weight are significantly different among males and females. Both variables are determined to have non-normal distributions, so the median is shown instead of the mean. The inter-quartile range (IQR) is shown instead of the standard deviation (SD) and the Wilcoxon rank sum test is conducted instead of the t-test.

Finally, pocket money was determined to be normally distributed and a t-test was carried out with a non-significant result. Note that for such a small sample size our conclusions are not so sound.

One can check the assumption for normality of residuals of 'money' by typing

```
> shapiro.test(lm(money ~ sex)$residuals)

        Shapiro-Wilk normality test

data:  lm(money ~ sex)$residuals
W = 0.8722, p-value = 0.08262
```

Moreover, the assumption of equal variance of residuals can be checked with

```
> bartlett.test(money ~ sex)

        Bartlett test of homogeneity of variances

data:  money by sex
Bartlett's K-squared = 5.8683, df = 1, p-value = 0.01542
```

Epicalc has preset the significance level for the Shapiro-Wilk and Bartlett tests to switch the results from using the t-test to using the Wilcoxon rank sum test at P>0.01, not P>0.05. The latest command has a P value of 0.015, not enough to activate this switching.

One can try with other variables in this dataset to get familiar with the reasons for choosing parametric and non-parametric tests. Users can also specify different output features, such as not showing statistical test results, the name of the test, and the variables to apply non-parametric statistical tests to. For example:

```
> tableStack(age:money, by=sex, test=FALSE)
> tableStack(age:money, by=sex, name.test=FALSE)
> tableStack(age:money, by=sex, iqr=c(age, money))
```

More examples

The 'by' argument in the `tableStack` function can also have more than 2 levels.

```
> data(Ectopic)
> use(Ectopic)
> des()

No. of observations = 723
  Variable      Class           Description
1 id            integer
2 outc          factor          Outcome
3 hia           factor          Previous induced abortion
4 gravi         factor          Gravidity

> table(outc)
outc
  EP   IA Deli
 241  241  241

> tableStack(hia:gravi, by=outc, var.labels=FALSE)
                  EP         IA       Deli        Test stat.  P value
3 : hia                                       Chi(2) = 78.72  < 0.001
   never IA  61(25.3)  110(45.6) 158(65.6)
   ever IA  180(74.7)  131(54.4)  83(34.4)

4 : gravi                                     Chi(4) = 46.18  < 0.001
   1-2      117(48.5)  121(50.2)  182(75.5)
   3-4       87(36.1)   85(35.3)   46(19.1)
   >4        37(15.4)   35(14.5)  13(5.4)
```

Note that when 'var.labels' is FALSE, the variable index and variable name is displayed instead of the variable label. While this is not ready to 'copy & paste' to the manuscript, it is useful for data exploration. An abnormal category for the row variables, such as wrong levels of labeling, or rows with too small numbers, may indicate a need to recode that variable before the final version can be used.

When the row variable is a factor, a cross-tabulation for that variable against the 'by' variable is displayed. The table indicates that there are 241 records of EP (women with an ectopic pregnancy). Out of these, 180 had a previous history of induced abortion, thus the prevalence is 74.7%. This is much higher than the corresponding IA group (54%) as well as in the delivery group (34%). The chi-squared test is highly significant (P < 0.001). For 'gravi', the percentage of having 1-2 previous pregnancies is highest in the 'Deli' group and the difference of gravidity is also highly significant. Association of the outcome (column variable) and more than one row variable suggests potential confounding problems that require further analysis.

These default settings of the arguments can always be overruled, such as setting the output of hypothesis testing to FALSE or showing column percentages.

```
> tableStack(hia:gravi, by=outc, test=FALSE)
                                 EP        IA      Deli
Previous induced abortion
   never IA                61(25.3) 110(45.6) 158(65.6)
   ever IA                180(74.7) 131(54.4)  83(34.4)
Gravidity
   1-2                    117(48.5) 121(50.2) 182(75.5)
   3-4                     87(36.1)  85(35.3)  46(19.1)
   >4                      37(15.4)  35(14.5)   13(5.4)
> tableStack(hia:gravi, by=outc, test=FALSE, percent="row")
```

Note that 'percent' should be set to "row" if we want to compare the percentage of the outcome variable which has been designated to the column variable.

The above two data frames have row variables consisting of only one type, either continuous variables or factors. Let's try with one with a mixture of both.

```
> data(Cars93, package="MASS")
> use(Cars93)
> des()
> tableStack(vars=4:25, by=Origin)
                          USA         non-USA  Test stat.    P value
Min.Price                                      Rank sum test   0.812
  median(IQR) 14.5(11.4,19.4)  16.3(9.1,22.9)

Price                                          Rank sum test   0.672
  median(IQR) 16.3(13.5,20.7) 19.1(11.6,26.7)

Max.Price                                      Rank sum test   0.489
  median(IQR)   18.4(15,24.5) 21.7(12.9,28.5)

MPG.city                                       Rank sum test   0.037
  median(IQR)       20(18,23)       22(19,26)

MPG.highway                                    Rank sum test   0.191
  median(IQR)       28(26,30)       30(25,33)

AirBags                                        Chi(2) = 0.48   0.786
  Driver & Passenger  9(18.8)         7(15.6)
  Driver only        23(47.9)        20(44.4)
  None               16(33.3)          18(40)
```

```
DriveTrain                                     Chi(2) = 0.17   0.919
  4WD                5(10.4)         5(11.1)
  Front             34(70.8)        33(73.3)
  Rear               9(18.8)         7(15.6)

Cylinders                                      Fisher's test   0.011
  3                     0(0)          3(6.7)
  4                 22(45.8)           27(60)
  5                     0(0)          2(4.4)
  6                 20(41.7)        11(24.4)
  8                  6(12.5)          1(2.2)
  rotary                0(0)          1(2.2)
================== remaining lines omitted =================
```

Some of the variables, such as those related to price, rate of fuel consumption and power, are either non-normally distributed or have a highly different variance between the two origins of cars, thus were tested with the non-parametric rank sum test. The other continuous variables are all tested with a t-test. There are four factor variables. Location of airbags (AirBags), type of drive train (DriveTrain) and availability of manual transmission (Man.trans.avail) were tested with a chi-squared test. On the other hand, number of cylinders (Cylinders) violates the assumptions of the chi-squared test, and so Fisher's exact test was used. The two-sided P-value is very small indicating that pattern of cylinders between cars of US and non-US origin is significantly different.

Colum of total

If required, an additional column of the total can be shown.

```
> tableStack(vars=4:25, by=Origin, total.column=TRUE)
```

In this case, omitting the test may look better.

```
> tableStack(vars=4:25, by=Origin, total.column=T, test=F)

                                 USA         non-USA          Total
Min.Price
  median(IQR)        14.5(11.4,19.4)  16.3(9.1,22.9) 4.7(10.8,20.3)

Price
  median(IQR)        16.3(13.5,20.7) 19.1(11.6,26.7) 7.7(12.2,23.3)

Max.Price
  median(IQR)          18.4(15,24.5) 21.7(12.9,28.5) 9.6(14.7,25.3)

MPG.city
  median(IQR)              20(18,23)       22(19,26)      21(18,25)

MPG.highway
  median(IQR)              28(26,30)       30(25,33)      28(26,31)

AirBags
   Driver & Passenger        9(18.8)         7(15.6)       16(17.2)
   Driver only              23(47.9)        20(44.4)       43(46.2)
   None                     16(33.3)          18(40)       34(36.6)
================== remaining lines omitted =================
```

In some occasions, only the total column is worth displaying. For example, in the **Compaq** dataset, the first table may be a description of information of the subjects on staging, age group, sex, etc.

```
> data(Compaq)
> use(Compaq)
> des()
> tableStack(vars=4:6, by="none")
                   Total
stage
   Stage 1     530(49.8)
   Stage 2     390(36.7)
   Stage 3       81(7.6)
   Stage 4       63(5.9)

Age group
   <40         296(27.8)
   40-49       285(26.8)
   50-59       243(22.8)
   60+         240(22.6)

ses
   Rich        279(26.2)
   High-middle   383(36)
   Poor-middle 154(14.5)
   Poor        248(23.3)
```

In fact, the "none" string can be replaced with any quoted value with the same results.

```
> tableStack(vars=4:6, by="junk")
```

Exporting 'tableStack' and other tables into a manuscript

R has a useful function to write a matrix, table or data frame into a comma separated variable (csv) file that is readable by Excel. After being read into Excel, the table can easily be copied into the manuscript.

```
> table1 <- tableStack(vars=4:25, by=Origin, data=Cars93)
> write.csv(table1, file="table1.csv")
> getwd()
```

The last command shows the current working directory, which should contain the file "**table1.csv**". Go to that directory and open the file in Excel to see the results. Then copy and paste the output table to your manuscript document.

This technique also works well with the *display* series of Epicalc, such as *regress.display*, *logistic.display*, etc.

```
> glm1 <- glm(Origin ~ Price + AirBags + DriveTrain, binomial,
  data=Cars93)
> logistic.display(glm1) -> glm1.display
> attributes(glm1.display)
$names
[1] "first.line" "table"      "last.lines"

$class
[1] "display" "list"

> table2 <- glm1.display$table

> write.csv(table2, file="table2.csv")
```

Then see what you get.

Chapter 28: Diagnostic test

Predicting a disease status: diagnostic test

In clinical medicine, one of the important tasks of a doctor is to decide whether the patient has the disease so that appropriate further action can be taken. When a certain test is carried out, the result is used to guide the decision. There are a few terms used to specify the quality of the test: sensitivity, specificity, and positive and negative predictive values. Since logistic regression is also used to predict an outcome, it is essential to understand these terms in order to use them to assess how well the regression can predict the outcome.

Sensitivity is defined as the probability of having a positive result given that the patient has the disease.

Specificity is defined as the probability of having a negative result given that the patient does not have the disease.

Positive predictive value is the probability of being diseased given that the test is positive.

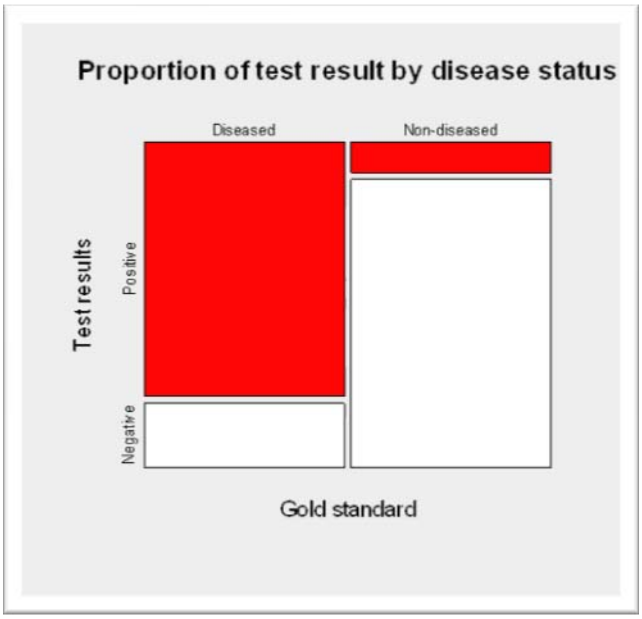
Negative predictive value is the probability of being non-diseased given that the test is negative.

Sensitivity and specificity are measured under a research setting with a gold standard or one which is assumed to be correct. In a diagnostic study, there are usually two groups of subjects recruited with known disease status: diseased and non-diseased. These subjects then undergo a test. Among the diseased, the sensitivity is the probability of having a positive test result. Among the non-diseased, the specificity is the probability of having a negative test result.

Let's assume that there are 100 diseased and 100 non-diseased in a study. Suppose also that for a particular diagnostic test the sensitivity is 80% and the specificity is 90%. In R, this can be illustrated as follows:

```
> table1 <- as.table(rbind(c(80,20), c(10,90)))
> dimnames(table1) <- list("Gold standard"=c("Diseased","Non-
  diseased"), "Test results"=c("Positive","Negative"))

> table1
```

```
              Test results
Gold standard  Positive Negative
  Diseased           80       20
  Non-diseased       10       90
> plot(table1, col=c("red","white"), main="Proportion of test
  result by disease status")
```



Graphical explanation of sensitivity, specificity, positive and negative predictive values

From the graph, sensitivity is the relative height of the shaded part of the left column (the diseased group) and specificity is the relative height of the unshaded part of the right column (the non-diseased group).

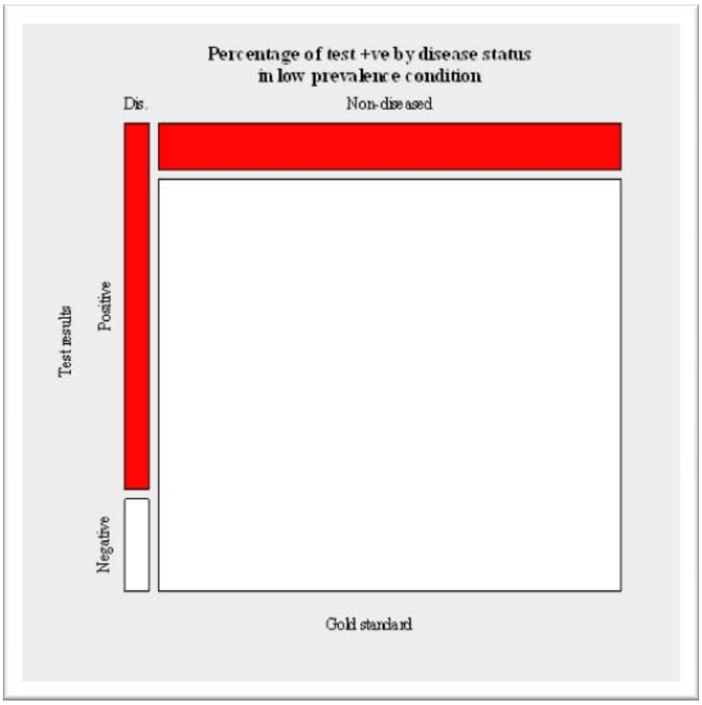
Positive predictive value is the proportion of shaded area in the left hand side area relative to all shaded areas. In this case it is 80/(80+10) or 0.89.

Negative predictive value is the proportion of unshaded area in the right hand side area relative to all unshaded areas. In this case it is 90/(20+90) or 0.818.

In fact, the relative width of the left-hand column reflects the prevalence of the disease. In this case it is 50% since both groups (diseased and non-diseased) are equal in number. Sensitivity and specificity are fixed to each column. They are therefore independent of the prevalence of the disease.

Outside the research condition, especially in community studies, the prevalence of diseased is usually much lower than 50%. Suppose the number of diseased is the same but since the testing is now done in a community setting we have more non-diseased, let's say with a prevalence of now only 5%. This can be illustrated as follows:

```
> table2 <- as.table(rbind(c(80,20), c(190,1710)))
> dimnames(table2) <- list("Gold standard" =c("Dis.", "Non-
  diseased"), "Test results"=c("Positive","Negative"))
> plot(table2, col=c("red","white"), main="Percentage of test
  +ve by disease status", cex=1)
> title(main="in low prevalence condition", line=.6)
```



The above graph denotes a low prevalence because the left hand column size is only one-twentieth of the whole width of the two columns combined. Sensitivity (80%) and specificity (90%) are unchanged from the previous example. However, the positive predictive value is now much smaller. Most of the shaded area is apportioned in the right hand column. The shaded area among the diseased group (left-hand column) is less than a half of the total shaded area. In fact, it is 80/(80+190) = 29.6%. This is the new positive predictive value. Under the condition of the prevalence being 5%, there is less than 30% chance that a person with a positive test result will have the disease. Making a clinical diagnosis of a rare disease in the community or population must be done with caution because the manifestation may actually come from other similar diseases.

Lowering the prevalence also has some effect on the negative predictive value. In the mosaic plot above, the amount of unshaded area in the right hand column is overwhelming. The negative predictive value is now 1710/(1710+20) = 98.8%. This is a rise from the previous value of 81.8%. The tendency to exclude the disease after obtaining a negative test result may not change the clinical decision very much. Therefore, in screening tests where the pre-test probability of the disease is already low, negative predictive value is of limited use.

In evaluation of a surveillance system, the number of cases detected is in the surveillance report. This could be conceptually represented by the two (red) shaded rectangles. The total number of diseased persons could be traced from clinical service records, which is represented by the left vertical column. These numbers would allow calculation of the sensitivity (left upper shaded rectangle divided by the whole left column) and positive predictive value (left upper shaded rectangle divided by all shaded areas) of the surveillance system. However, with population dynamics (birth, death and migration) the number of non-diseased subjects is usually unknown or the right vertical column is not defined. In such cases, the specificity and negative predictive value cannot be determined.

Test of more than one level

Many laboratory tests (such as level of serum biomarkers) give results as a value on a continuous scale. Using different cut-points would give different values for the sensitivity and specificity. A conservative cut-point (one set at a high level thus reducing almost all false positives) has high specificity. However, a disadvantage is having more false negatives. The reverse is true when the cut-point is relaxed (moved to a low level).

In the example for `roc.from.table` function in the **epicalc** package, the fictitious test is an ordinal hypothetical variable, say, age in years. Cross-tabulation with the disease status (100 subjects in each group) yields the following results.

```
> table1 <- as.table(cbind(c(1,27,56,15,1),c(0,0,10,69,21)))
> colnames(table1) <- c("Non-diseased", "Diseased")
> rownames(table1) <- c("15-29","30-44","45-59","60-89","90+")
> table1

      Non-diseased Diseased
15-29            1        0
30-44           27        0
45-59           56       10
60-89           15       69
90+              1       21
```

From the table above, it is reasonably clear that subjects with higher ages are more likely to be diseased. Suppose we set the cut-point at above 29 years. All diseased are older than this cut-point. None of them would have false negative results. The sensitivity is thus 100%. However, only one of the 100 non-diseased has a true negative value. Specificity is therefore 1%. If we move the cut-point to above 44, the sensitivity is still 100% but the specificity increases to (1+27)/100 = 28%. Subsequently, as the values of the cut-points increase further, the sensitivity decreases to 90% and then 21% while the specificity increases to 84% and then 99%. This "sliding scale" between sensitivity and specificity, known as a diagnostic table, is automatically generated by the function `roc.from.table`.

```
> roc.from.table(table1)
$auc
[1] 0.8963

$original.table
      Non-diseased Diseased
15-29            1        0
30-44           27        0
45-59           56       10
60-89           15       69
90+              1       21

$diagnostic.table
        1-Specificity Sensitivity
                 1.00        1.00
> 15-29          0.99        1.00
> 30-44          0.72        1.00
> 45-59          0.16        0.90
> 60-89          0.01        0.21
> 90+            0.00        0.00
```

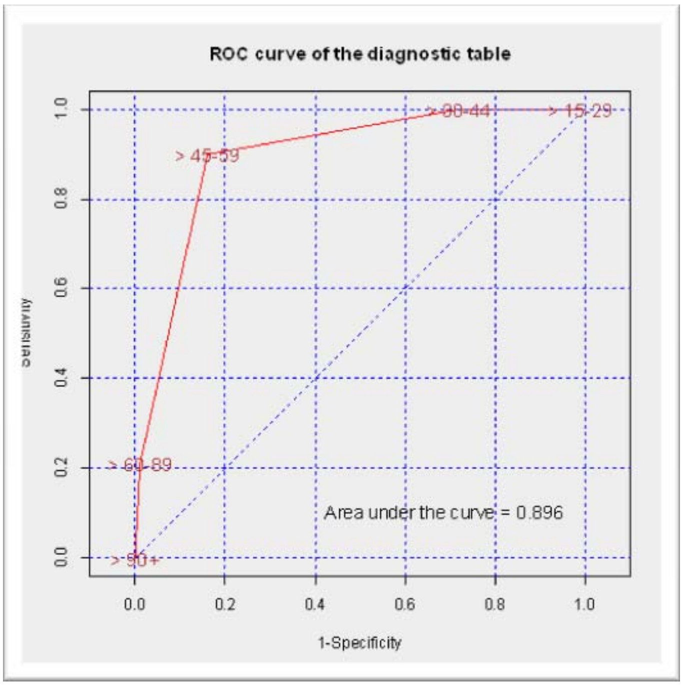
The text output has three components: AUC or area under the curve, the original table and the diagnostic table.

The orientation of the table must conform to R principles. Values of the rows increase as one moves from the top to the bottom, and values of the columns increase as one moves from the left to the right. The original table must have non-diseased on the left column and diseased on the right column. Usually the disease status is a numeric or coded (factor) variable having non-diseased value lower or before diseased. For example, non-diseased=0 and diseased=1, or non-diseased=1 and diseased=2. If disease status is a factor then non-diseased must be the first level. Similarly, the values of the test must be sorted in ascending order so that the highest value is at the bottom of the row. Any deviation from this principle may result in incorrect results.

Note that in the diagnostic table, the first column is 1-specificity rather than specificity itself. This column is used for the X axis in the plot, while the sensitivity is used for the Y axis. The plot is called an ROC (Receiver Operating Characteristic) curve. The plot is produced with the following commands.

```
> roc.from.table(table1, title=TRUE, auc.coords=c(.4,.1),
  cex=1.2)
> roc1 <- roc.from.table(table1, graph=FALSE)
> n <- nrow(roc1$diagnostic.table)
> cut.points <- rownames(roc1$diagnostic.table)[-c(1,n)]
> text(x=roc1$diagnostic.table[-c(1,n),1],
  y=roc1$diagnostic.table[-c(1,n),2], labels=cut.points,
  cex=1.2, col="brown")
```

The first line above produces the plot, specifying the display of the automatic graph title and the AUC value at the given coordinates – with a 20% character expansion factor (cex=1.2). The second command saves results of the function `roc.from.table` as an R object so that the row names of the diagnostic table (the cut-points) can be used to label the curve at the cut-points. The greater than sign ">" in front of the cut-point means that any test value higher than that "bin" is considered as positive. Thus, the label "`> 45-59`" from the '$diagnostic.table' component in the output above includes only two rows, "`> 60-89`" and "`> 90+`" as positive. Here the sensitivity is 90% and the specificity is 16%.



Area under the curve (AUC)

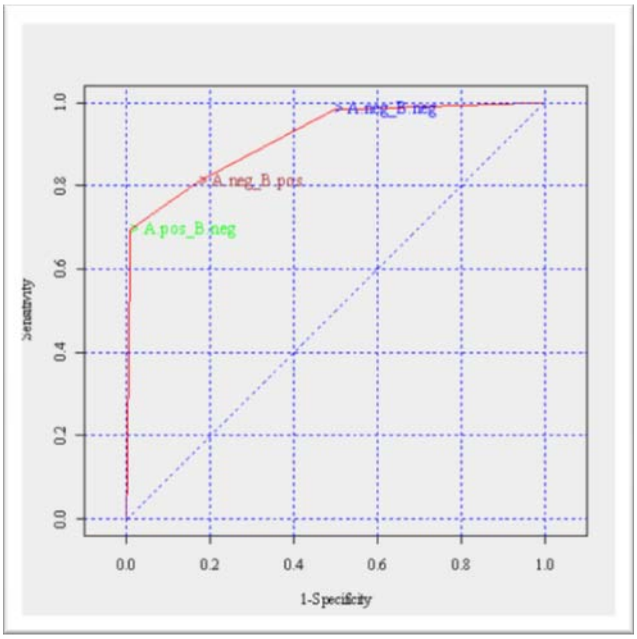
The `roc.from.table` function computes and returns the AUC of the ROC curve. The higher the AUC, the better the test could be used to discriminate diseased from non-diseased subjects. When the AUC is equal to 0.5, the test has absolutely no discrimination power.

Multiple tests

In clinical practice, the doctor often employs more than one test to the patient to diagnose one particular disease. This is not much different from applying more than one risk factor in predicting a health outcome. If there are two tests, A & B, each of which is dichotomized, there would be 4 possible test results, ie. both negative, A negative and B positive, A positive and B negative, and both positive.

Let's simulate this scenario.

```
> testA <- gl(n=2,k=2,length=4,labels=c("A.neg","A.pos"))
> testB <- gl(n=2,k=1,length=4,labels=c("B.neg","B.pos"))
> data1 <- data.frame(testA, testB,
  non.diseased=c(312,200,100,5), diseased=c(3,30,20,120),
  row.names = paste(testA,testB, sep="_"))
> data1
            testA testB non.diseased diseased
A.neg_B.neg A.neg B.neg          312        3
A.neg_B.pos A.neg B.pos          200       30
A.pos_B.neg A.pos B.neg          100       20
A.pos_B.pos A.pos B.pos            5      120

> roc.from.table(data1[,3:4]) # auc = 0.9163114
> roc.from.table(data1[,3:4]) -> roc2
> n <- nrow(roc2$diagnostic.table)
> d.table <- roc2$diagnostic.table[-c(1,n),]
> cut.points2 <- row.names(d.table)
> text(x=d.table[,1], y=d.table[,2],
  labels=cut.points2, cex=1.2,
  col=c("blue","brown","green"), adj=0)
```



In a serial test, both tests must be positive in order to have a final positive test. Otherwise, the test is negative. This corresponds to the cut-point of "`>A.neg_B.neg`" shown in blue colour in the ROC curve above. In this situation, the sensitivity is very high (98.2%) but the specificity is only moderate (49.4%).

In a parallel test, if any test is positive then the final result is a positive test. The final test result is considered negative only when both test results are negative ("`>A.pos_B.neg`" shown in green colour in the ROC curve). In this case, the sensitivity is acceptable (69.4%) while the specificity is very high (>99%). In this hypothetical dataset a parallel test may be the best choice.

ROC curve from logistic regression

Sometimes, the analyst may want to draw an ROC curve from the results of a logistic regression model to check how well the model distinguishes cases from controls. Let's use the **`infert`** dataset from the **datasets** package in R.

```
> model.a <- glm(case ~ induced + spontaneous, data=infert,
  family=binomial)
> logistic.display(model.a)
Logistic regression predicting case
                         crude OR(95%CI)  adj. OR(95%CI)
  P(Wald's test) P(LR-test)
induced (cont. var.)     1.05 (0.74,1.5)  1.52 (1.02,2.27)
  0.042          0.042
spontaneous (cont. var.) 2.9 (1.97,4.26)  3.31 (2.19,5.01)  <
  0.001        < 0.001
```

The model treats all independent variables as continuous. Thus, one additional induced abortion increases the risk of infertility by 50% and one additional spontaneous abortion increases the odds more than 3 times. Now, let's draw the ROC curve.

```
> lroc(model.a, line.col="red", lwd=3)
$model.description
[1] "case ~ induced + spontaneous"
$auc
[1] 0.7285506
$predicted.table
 predicted.prob Non-diseased Diseased
         0.1534           60        7
         0.2158           33       12
         0.2949           20        9
         0.3750           25       22
         0.4768           11        5
         0.5806            4        4
         0.6651           11       18
         0.7511            1        6

$diagnostic.table
   1-Specificity Sensitivity
```

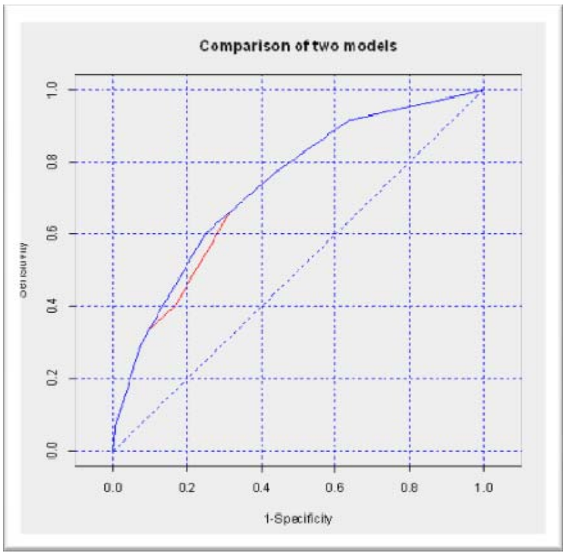
```
     1.000000000  1.00000000
>    0.636363636  0.91566265
>    0.436363636  0.77108434
>    0.315151515  0.66265060
>    0.163636364  0.39759036
>    0.096969697  0.33734940
>    0.072727273  0.28915663
>    0.006060606  0.07228916
>    0.000000000  0.00000000
```

Look at the predicted table above. As both induced and spontaneous abortion have 3 possible values in the data set (0, 1 and 2), there are 9 possible combinations of the independent variables. Each level of the combinations has its own probability of a subject in that level being a case. The values of these probabilities, which have been automatically sorted, are used to name the rows of the predicted table.

We now fit another model with the independent variables converted to factors and an interaction term added.

```
> model.b <- glm(case ~ factor(induced) * factor(spontaneous),
  data=infert, family=binomial)
> lroc(model.b, line.col="blue", lwd=2, add=TRUE)$auc
[1] 0.7370938
> title(main="Comparison of two models")
```

Note that the second last command includes the argument "add" which is set to TRUE. Both the `lroc` and `roc.from.table` functions have this option which allows the user to draw a new ROC curve on top of an existing one. A blue line from 'model.b', which contains the interaction terms, is added to the graph and almost obscures the red line. As seen from the output, and in this case the graph, 'model.b' gives a higher AUC value.



Although the AUC of the ROC curve is useful information, it should *not* be used to compare models, especially between one containing continuous variables to one which contains factors without interaction terms. For example

```
> model.c <- glm(case ~ factor(induced) + factor(spontaneous),
  data=infert, family=binomial)
> lroc(model.c, graph=FALSE)$auc
[1] 0.7285506
```

The AUC values of both 'model.a' and 'model.c' are the same because cross-tabulation between the real outcome and the predicted probability of both models yields the same table. (Only the row names are different).

A more reliable method of comparison is to use the AIC (Akaike's information criterion) or to perform a likelihood ratio test.

```
> AIC(model.a); AIC(model.c)
[1] 285.612
[1] 289.4693

> lrtest(model.a, model.c)
Likelihood ratio test for MLE method
Chi-squared 2 d.f. =  0.1426627 , P value =  0.9311533
```

The output implies that 'model.a' is more efficient as it gives a lower value AIC. However, since the p-value from the likelihood ratio test is large, there is not enough evidence to conclude that the two models are significantly different.

References

Hanley JA, McNeil BJ. The meaning and use of the area under the Receiver Operating Characteristic (ROC) curve. Radiology 1982; 143, 29-36.

Chapter 29: Statistics on agreement

Nature of reliability and agreement in assessment

Epidemiology and statistics are quantitative sciences, basing their conclusions on quantity of measurements. Quantity comes from reports of instruments or human observations. Sources of variation of reports depend on what have been measured and the assessors (instrument and/or observer). Variation of measurements due to assessors may be within the same assessor or between different assessors. It is important to determine these sources of variation in order to improve the quality of research.

Reliability, in psychometrics, refers to the property of two or more assessments giving the same or close value, if the assessment is done on the same subject. In chapter 23, we computed Cronbach's alpha for the **Attitudes** dataset. This number is sometimes called a reliability coefficient since it reflects the level of closeness of values reported using different items from the questionnaire. The closeness is however measured based on only a single interview from one individual.

Test-retest reliability is also based on the same person but at different times. Statistically, this is simply the correlation. An ideal measurement would have a test-retest coefficient close to unity, which would indicate that the test has good quality.

Regression dilution bias due to imperfect test-retest reliability

An analytic study having a key independent variable with a low test-retest reliability coefficient will be biased toward the null hypothesis. To explain this direction of bias, suppose that, in general, variable X is influenced by variable Y with a certain level of regression of the slope. With poor reliability of X, each X is randomly shifted away from it real value. The degree of slope under this condition will be reduced toward zero, which leads the conclusion toward the null hypothesis. The following R commands illustrate this concept.

First, set the random number seed so that readers can replicate the results.

```
> set.seed(50)
```

Next, generate a vector of 10 random numbers from a population with a mean of 0 and a standard deviation of 1.

```
> x <- rnorm(10)
```

Then, create another vector by adding random numbers from the same population above to the previous vector.

```
> x1 <- x + rnorm(10)
```

Now repeat the process with a new seed.

```
> set.seed(100)
> x2 <- x + rnorm(10)
```

The correlation between 'x1' and 'x2' is found by

```
> cor(x1,x2)
[1] 0.7583999
```

The two vectors are highly correlated.

Now create another vector using the following simple equation.

```
> y <- 2*x + 0.5
```

The vector 'y' will have a linear relationship with 'x' without any error. This is shown by regressing 'y' on 'x'.

```
> lm(y ~ x)
Coefficients:
(Intercept)            x
        0.5          2.0
```

The coefficient of 'x' is 2 meaning that a one unit increase of 'x' will result in 'y' increasing by two units.

Now plot these vectors with lines of best fit superimposed. Try each command one by one and look at the graphics window.

```
> plot(x, y, xlim=c(-3,3), ylim=c(-6,6), cex=2)
> abline(lm(y ~ x), lty=2)
```

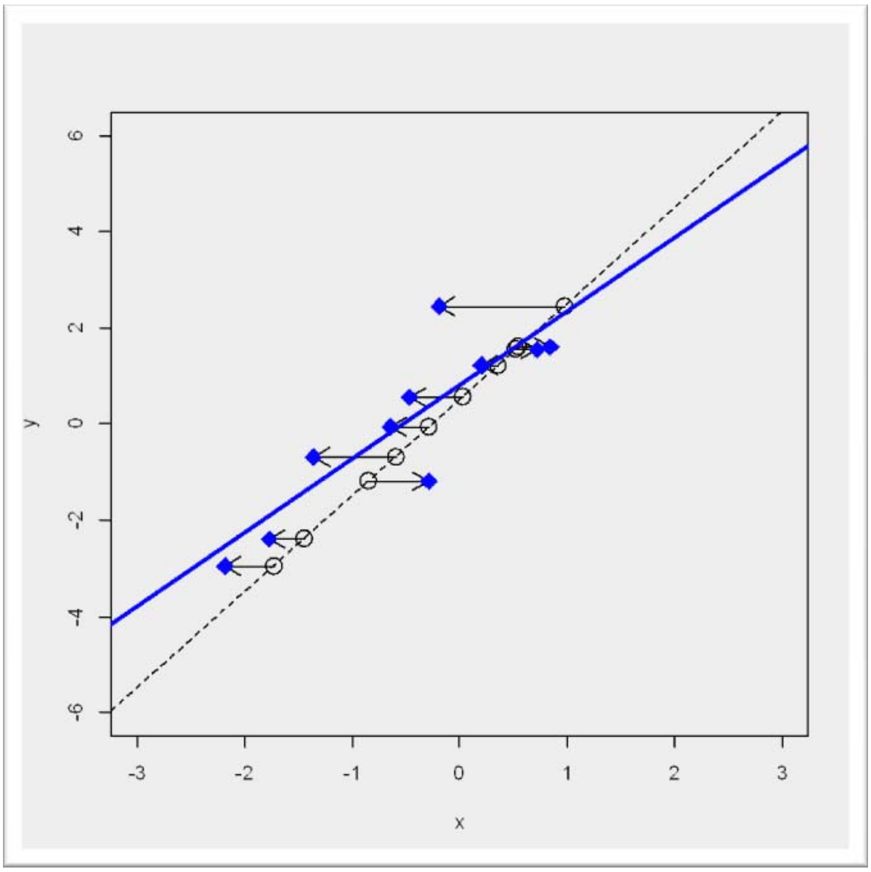
As expected, the line is a perfect fit to the points. Now show the 'x1' values.

```
> points(x1, y, pch=18, col="blue",cex=2)
> arrows(x0=x, y0=y, x1=x1, y1=y, length=0.15)
```

The arrows show how much 'x' differs from 'x1'.

A regression of 'y' on 'x1' is performed and the line of best fit is again superimposed on the plot.

```
> lm1 <- lm(y ~ x1)
> abline(lm1, col="blue", lty=1, lwd=3)
```



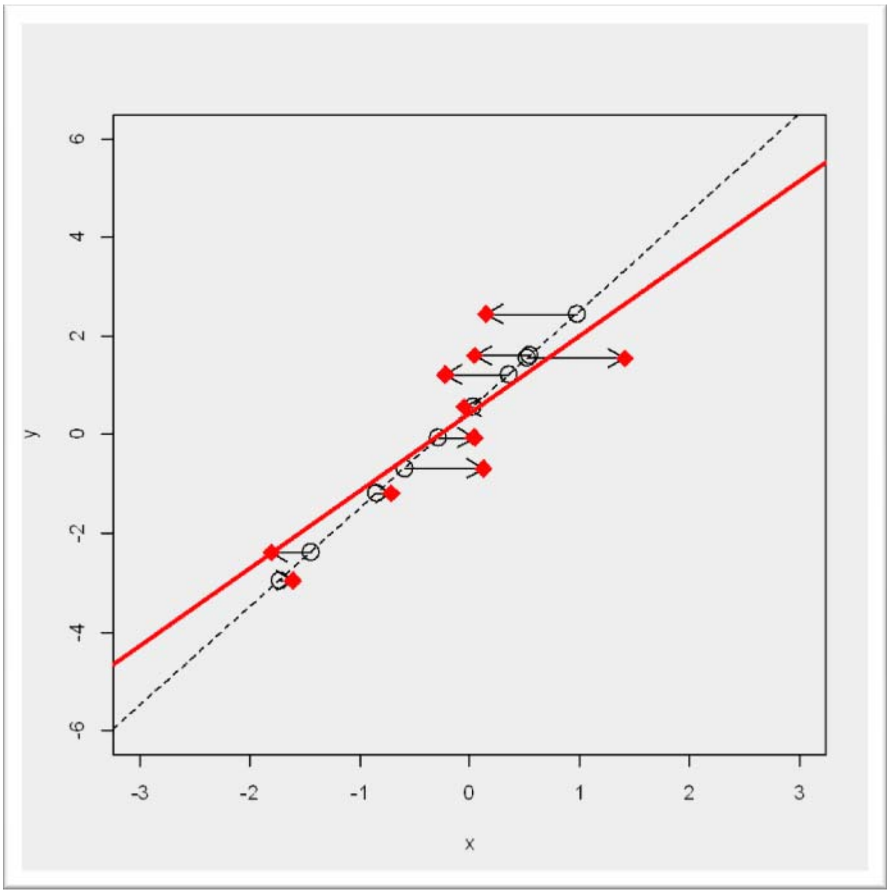
Note that the slope of the solid blue line is flatter than the dashed black line. The coefficient of 'x1' from the model is given by

```
> coef(lm1)
(Intercept)          x1
  0.7990983   1.5364922
```

The value is approximately 1.5, which is less than that of 'x'.

We can further test the effect on regression using 'x2' instead of 'x and we should see similar results.

```
> plot(x,y, xlim=c(-3,3), ylim=c(-6,6), cex=2)
> abline(lm(y ~ x), lty=2) # again a perfect fit
> arrows(x0=x, y0=y, x1=x2, y1=y, length=0.15)
> points(x2,y, pch=18, col="red", cex=2)
> lm2 <- lm(y ~ x2)
> abline(lm2, col="red", lty=1, lwd=3)
> coef(lm2)
(Intercept)          x2
  0.4239088   1.5725094
```



The coefficient of 'x2' is very similar to 'x1' since the values of 'x2' deviate from 'x' by a similar amount as 'x1' deviates from 'x'. We can generate more vectors, 'x3', 'x4' etc by adding random amounts to 'x'. The higher the amount added, the lower the value of the coefficient of 'x' will be and the flatter the regression line will be.

The implication of these findings is that if the independent variable has random fluctuating values, or if two measurements on the same person but at different times are not well correlated, a regression based on a measurement at one point of time will be biased toward the null hypothesis. The regression line will be flattened and the coefficient of that variable will be biased toward zero. The P value will be biased toward one. All of this is called ‘regression dilution bias’.

It is therefore useful to do a small test-retest study. A low correlation indicates that the level of fluctuation is high and the effect of regression dilution bias is high. The way to correct this bias is beyond the scope of this chapter.

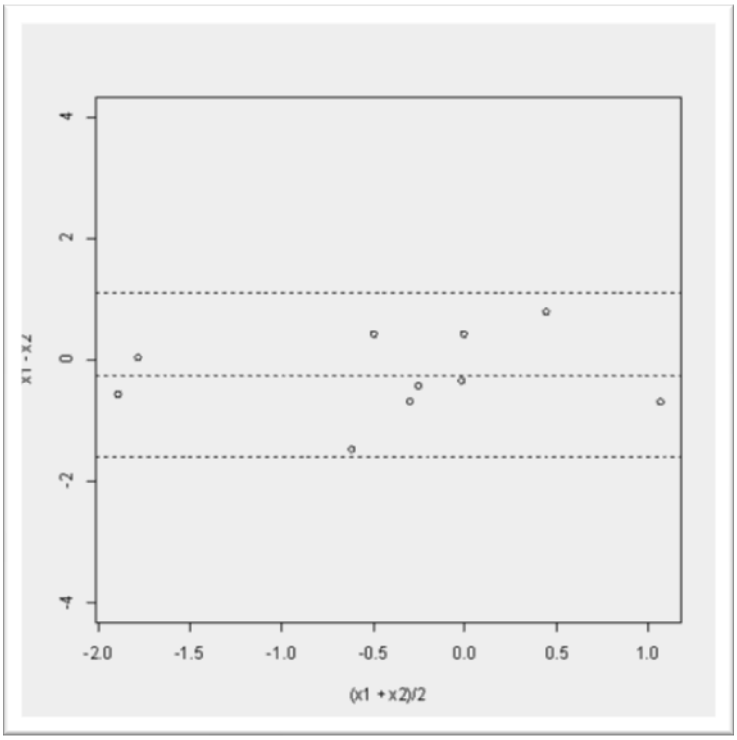
Bland-Altman plot

Instead of looking at correlation, one can compare two series of observations by looking at the vector of the difference.

```
> summ(x1-x2)
  obs. mean   median  s.d.   min.   max.
  10   -0.25  -0.38   0.68   -1.48  0.797
```

One could simply plot these values on a graph but a better way to display these differences is to plot them against the mean of the individual pairs.

```
> plot((x1+x2)/2, x1-x2, ylim=c(-4,4))
> abline(h=mean(x1-x2) - c(-2,0,2)*sd(x1-x2), lty=2)
```



This is called Bland-Altman plot. The middle line is the mean difference while the two extreme lines are plus and minus two standard deviations. The above points have a relatively flat distribution. It does not suggest a strong relationship between the differences and the means of individual pairs of points.

```
> cor((x1+x2)/2, x1-x2)
[1] 0.1243239
```

Correlation vs difference

In fact, the correlation coefficient is the covariance of the standardized values of two variables. The term "standardize" means to transform the values by subtracting the mean from the original values and dividing by the standard deviation. We can write a function to standardize a vector as follows.

```
> standardize <- function(x) (x-mean(x))/sd(x)
```

Now let’s examine the covariance and correlation of 'x1' and 'x', defined previously.

```
> cov(x1,x2)
[1] 0.7090834

> cor(x1,x2)
[1] 0.7583999
```

They are very similar but not exactly the same. This is because both 'x1' and 'x2' were (randomly) sampled from a standard normal population with mean 0 and standard deviation 1. But neither the mean of 'x1' nor 'x2' is equal to 0 nor are their standard deviations equal to 1. Now we compute the covariance of their standardized values.

```
> cov(standardize(x1), standardize(x2))
[1] 0.7583999
```

The result is exactly the same as what was obtained from the command `cor(x1,x2)` above.

Now, let’s create a vector which has a higher correlation with 'x1'.

```
> x3 <- 3*x1 + rnorm(10, sd=0.1)
> cor(x1,x3)
[1] 0.9996497
```

Both 'x1' and 'x3' have almost a perfect correlation because the random values that were added have a relatively small standard deviation. When the two values are displayed on a scatterplot, the points almost form a straight line.

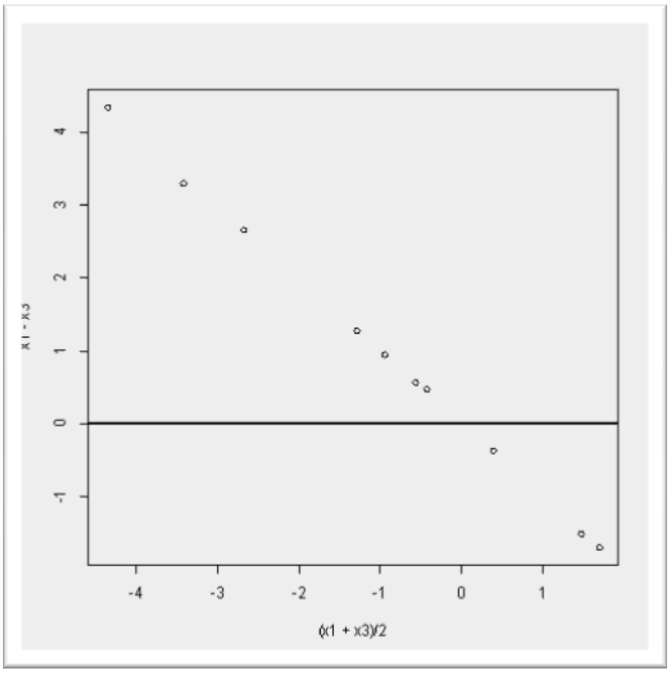
```
> plot(x1, x3)
```

However, the differences between 'x1' and 'x3' are large because they have relatively different scales.

```
> summ(x1-x3)
  obs. mean   median  s.d.   min.   max.
  10   1.001  0.758   1.98   -1.699 4.354
```

The difference between 'x1' and 'x3' is greater than that between 'x1' and 'x2'.

```
> plot((x1+x3)/2, x1-x3)
> abline(h=0, lwd=2)
```



The Bland-Altman plot for this pair of vectors reveals a large negative correlation between the differences and means of the individual pairs. The difference decreases as the mean increases.

```
> cor((x1+x3)/2, x1-x3)
[1] -0.9997976
```

The vector 'x2' is less correlated with 'x1' than 'x3' is. However, 'x3' is on different scale to 'x1'. Between 'x2' and 'x3', which one has stronger agreement with 'x1'?

The answer is 'x3' but it must be rescaled. 'x3', if scaled down by 2, will be a near perfect replacement of 'x1'.

Intra-class correlation and agreement in rating

Now we change over focus to agreement in rating. Often there is more than one rater. Each rater rates the same set of subjects. The rating scale often ranges from 1 to 5, just like in the **Attitudes** dataset of **epicalc**. Another good example dataset comes from the **psy** package. Install the package and load the **`expsy`** dataset. We will learn how to use and interpret the output from the important function `icc` together.

```
> library(psy)
> data(expsy)
> head(expsy)
  it1 it2 it3 it4 it5 it6 it7 it8 it9 it10 r1 rb1 r2 rb2 r3 rb3
1  NA   2   2   1   1   0   3   1   2    3 NA  NA  3   1  3   1
2   3   1   1   2   1   0   3   1   2    3  3   1  3   1  3   1
3   3   1   1   0   2   0   3   1   2    3  3   1  2   0  2   0
4   4   1   0   2   1   1   4   1   1    2  4   1  4   1  4   1
5   4   1   0   2   1   1   3   1   1    2  3   1  3   1  3   1
6   3   2   0   1   2   2   3   1   2    3  3   1  2   0  4   1
```

The following background information comes from the help file for this dataset. "The **expsy** data frame has 30 rows and 16 columns with some missing data noticeable. Columns it1 – it10 correspond to the rating of 30 patients with a 10 item scale. r1, r2, r3 correspond to the rating of item 1 by 3 different clinicians of the same 30 patients".

Let's calculate the intra-class correlation for the ratings of item 1 by these three raters.

```
> icc(expsy[,c(11,13,15)])
$nb.subjects
[1] 29
$nb.raters
[1] 3
$subject.variance
[1] 0.5574713
$rater.variance
[1] 0.002463054
$residual
[1] 0.1699507
$icc.consistency
[1] 0.7663657
$icc.agreement
[1] 0.7637795
```

There are two types of intra-class correlations: one for consistency among raters and one for agreement among raters. For details of the formula one can simply type:

```
> icc
```

The output is omitted here to save space.

The function is very transparent. It first modifies the dataset, which is originally in wide form (one unique subject per record) to be in long form (one score per record) to allow a linear regression and analysis of variance (anova) to be performed. The inter-subject variance and inter-rater variance are obtained from the results of the anova.

In this example, the rater is considered as the *class*. Intra-class correlation means correlation within the same rater. If the inter-subject variance contributes the majority of the total variance, the remaining variance, which includes the inter-rater variance, would therefore be comparatively low. In this case we can say that there would be relatively good agreement among the raters.

If the inter-rater variance is not included in the denominator for calculation of the intra-class correlation, the value just reflects consistency within the same rater. Thus, the value of '$icc.agreement' is always smaller than that of '$icc.consistency'. The level of consistency within the same person (rater) is always higher than the level of agreement among them.

Agreement on classification between two raters: the kappa statistic

When two raters are asked to classify subjects into non-ordered categories, calculation of the intra-class correlation is irrelevant. The appropriate measure of agreement is the kappa statistic.

We start with a binary classification, say columns 12 and 14 in the **`expsy`** data frame. Both the `ckappa` command from the **psy** package and the `kap.2.raters` command from **epicalc** give the same result.

```
> ckappa(expsy[,c(12,14)])
$table
  0  1
0 6  0
1 4 19

$kappa
[1] 0.6627907

> kap.2.raters(expsy[,12], expsy[,14])
      rater2
rater1  0  1
     0  6  0
     1  4 19

Observed agreement = 86.21 %
Expected agreement = 59.1 %
Kappa = 0.663
Standard error = 0.175 , Z = 3.791 , P value = < 0.001
```

Of these 30 subjects classified by the two raters into categories 0 or 1, 6 subjects were rated as 0 by both raters and 19 were rated as 1 by both raters, giving a total agreement of (6+19)/29 = 86.21%. In fact, rater 1 could have randomly chosen 6 (6+0) subjects out of these 29 and rater 2 could have chosen 10 (6+4) and so the expected agreement is thus {6/29*10 + (4+19)/29*(19+0)}/29 = 59.1%.

The maximum possible agreement is 100%. The kappa statistic is the proportion of agreement beyond chance over maximum possible agreement beyond chance. In this case, the former would be 86.21% – 59.1% and the latter would be 100% – 59.1%. Thus kappa = (86.21 – 59.1)/(100 – 59.1) = 0.663.

In epicalc, one can also obtain the kappa statistic directly from a table.

```
> table1 <- table(expsy[,12], expsy[,14])
> table1
> kap(table1)
```

The result is the same as above. When there are more than two categories, the command and the interpretation is the same.

```
> ckappa(expsy[,c(11,13)])
$table
  1 2 3 4
1 1 0 0 0
2 1 4 0 0
3 0 4 9 2
4 0 0 2 6

$kappa
[1] 0.5421053

> kap.2.raters(expsy[,11], expsy[,13])
      rater2
rater1 1 2 3 4
     1 1 0 0 0
     2 1 4 0 0
     3 0 4 9 2
     4 0 0 2 6

Observed agreement = 68.97 %
Expected agreement = 32.22 %
Kappa = 0.542
Standard error = 0.118 , Z = 4.58 , P value = < 0.001
```

In fact, the 12th and the 14th columns are binary transformed values of the 11th and the 13th columns. That’s why the two results are very similar. It should be noted that when there are more categories, the value of kappa will decrease because the probability of agreement will decrease. We save 'table2' for later use.

```
> table2 <- table(expsy[,11], expsy[,13])
```

Kappa statistic for ordinal variables

The above analysis is based on the criterion that if two raters classify the same person to a different category, they would be considered as disagreeing. When the rating variable is ordinal, classifications that are close to each other in order can be considered as being partial agreement. Since perfect disagreement is 0 and perfect agreement is 1, partial agreement would be given a weight somewhere between 0 and 1. The weighting scheme can be linear or quadratic.

```
> kap(table2, wttable="w")

 Table for calculation of kappa

   1 2 3 4
```

```
  1 1 0 0 0
  2 1 4 0 0
  3 0 4 9 2
  4 0 0 2 6

Observed agreement = 89.66 %
Expected agreement = 69.76 %
Kappa = 0.658
Standard error = 0.125 , Z = 5.276 , P value = < 0.001
```

Both the proportion of agreement and the kappa statistic have increased. When 'wttable' = "w" the weights are given by

$$1 - \mathrm{abs}(i - j)/(1 - k)$$

where i and j index the rows and columns of the ratings and k is the maximum number of possible ratings. A weight of 1 indicates an observation of perfect agreement. The result has a higher expected agreement and higher kappa value.

The weighting matrix can be shown as follows.

```
> kap(table2, wttable="w", print.wttable = TRUE)

          1         2         3         4
  1 1.0000000 0.6666667 0.3333333 0.0000000
  2 0.6666667 1.0000000 0.6666667 0.3333333
  3 0.3333333 0.6666667 1.0000000 0.6666667
  4 0.0000000 0.3333333 0.6666667 1.0000000
```

Note that there are 2 steps of partial agreement. The two weights are 1/3 and 2/3 with the higher values closer to the diagonal line of perfect agreement. Thus, two raters who disagree by only 1 category would be given a weight of 2/3. In other words, the number of subjects in which the two raters disagreed by only one category would be multiplied by 2/3 and included in the overall calculation of agreement. Similarly, the number of subjects who were classified as 1 and 3, or as 2 and 4 by the 2 raters would be multiplied by 1/3 and also added to the overall calculation of agreement.

The other weighting scheme is "w2" which is given by

$$1 - [\mathrm{abs}(i - j)/(1 - k)]^2$$

```
> kap(table2, wttable="w2")

 Table for calculation of kappa

    1 2 3 4
  1 1 0 0 0
  2 1 4 0 0
  3 0 4 9 2
  4 0 0 2 6
```

```
Observed agreement = 96.55 %
Expected agreement = 84.19 %
Kappa = 0.782
Standard error = 0.179 , Z = 4.357 , P value = < 0.001
```

Both expected agreement and kappa value are larger than those using a linear weighting scheme. The weight matrix is shown as follows:

```
> kap(table2, wttable="w2", print.wttable = TRUE)

          1         2         3         4
  1 1.0000000 0.8888889 0.5555556 0.0000000
  2 0.8888889 1.0000000 0.8888889 0.5555556
  3 0.5555556 0.8888889 1.0000000 0.8888889
  4 0.0000000 0.5555556 0.8888889 1.0000000
```

Under this quadratic weighting scheme, the weights are higher than for the linear weighting scheme. This weighting scheme gives the highest value of kappa.

Non-ordinal partial agreement

In the help page of the `kappa` function in epicalc, two surgeons rate 146 biopsies from patients suspected of having cancer. The commands are given below.

```
> class  <- c("Normal","Benign","Suspect","Cancer")
> raterA <- gl(4,4, label=class)
> raterB <- gl(4,1,16, label=class)
> freq   <- c(50,2,0,1,2,30,4,3,0,0,20,1,1,3,4,25)
> table1 <- xtabs(freq ~ raterA + raterB)
```

Without any weighting, the results are obtained as follows.

```
> kap(table1)

 Table for calculation of kappa
         raterB
raterA    Normal Benign Suspect Cancer
  Normal      50      2       0      1
  Benign       2     30       4      3
  Suspect      0      0      20      1
  Cancer       1      3       4     25

Observed agreement = 85.62 %
Expected agreement = 26.98 %
Kappa = 0.803
Standard error = 0.049 , Z = 16.461 , P value = < 0.001
```

A specimen rated as "normal" would suggest that surgical intervention would not be required. A benign tumor should be completely removed. If cancer is suspected, the surgical removal should be more extensive. Finally, if the biopsy is rated as cancerous, radiation and other procedures may be warranted. Thus the weight for two raters giving classifications of "Cancer" and "Suspect" should be fairly high (0.8) and moderate (0.5) for "Normal" and "Benign". Otherwise, the weight should be zero. In this case, the weight table could be prepared as follows.

```
> wt <-c(1,.5,0,0,.5,1,0,0,0,0,1,.8,0,0,.8,1)
> wttable <- xtabs(wt ~ raterA + raterB)
> wttable # Agreement between benign vs normal is .5, suspect
  vs cancer is .8
```

To compute kappa, type the following command:

```
> kap(table1, wttable=wttable, print.wttable=TRUE)

 Table for calculation of kappa
         raterB
raterA    Normal Benign Suspect Cancer
  Normal      50      2       0      1
  Benign       2     30       4      3
  Suspect      0      0      20      1
  Cancer       1      3       4     25

Weighting scheme
         raterB
raterA    Normal Benign Suspect Cancer
  Normal     1.0    0.5     0.0    0.0
  Benign     0.5    1.0     0.0    0.0
  Suspect    0.0    0.0     1.0    0.8
  Cancer     0.0    0.0     0.8    1.0

Observed agreement = 89.73 %
Expected agreement = 42.02 %
Kappa = 0.823
Standard error = 0.06 , Z = 13.673 , P value = < 0.001
```

The kappa statistic increases only slightly compared to the one without weighting, mainly because the cell counts for disagreement are relatively small.

In conclusion, weighting plays an important role in computing the kappa statistic when there are more than two ordered categories. Ignoring partial agreement will bias the result toward low agreement. A quadratic weighting scheme, on the other hand, may exaggerate the agreement. Weighting non-ordinal outcomes for partial agreement must therefore be done with care.

More than two raters on a categorical classification

In the **`expsy`** dataset, there were more than two raters but the rating scale was continuous. An example where the outcome is categorical is now given.

The calculation of the kappa statistic for more than two raters when the outcome is categorical uses a different approach to when the outcome is continuous. Although the dataset may specify how each rater rated an individual, in the analysis, the raters are all ignored. Only the frequency distribution of the category for each individual is used in the calculation.

From the example in the help page for the `kap` function, we create a dataset of 5 raters who rated 10 subjects using 3 possible classification categories. The commands are given below.

```
> category.lab <- c("yes","no","Don't know")
> rater1 <- factor(c(1,1,3,1,1,1,1,2,1,1),
  labels=category.lab)
> rater2 <- factor(c(2,1,3,1,1,2,1,2,3,1),
  labels=category.lab)
> rater3 <- factor(c(2,3,3,1,1,2,1,2,3,1),
  labels=category.lab)
> rater4 <- factor(c(2,3,3,1,3,2,1,2,3,3),
  labels=category.lab)
> rater5 <- factor(c(2,3,3,3,3,2,1,3,3,3),
  labels=category.lab)
```

The command to calculate the kappa statistic is:

```
>
  kap.m.raters(raters=data.frame(rater1,rater2,rater3,rater4,r
  ater5))
Each category:
           kappa std.error    z p.value
yes        0.292       0.1 2.92   0.002
no         0.671       0.1 6.71 < 0.001
Don't know 0.349       0.1 3.49 < 0.001

Overall:
           kappa std.error    z p.value
           0.418     0.072 5.83 < 0.001
```

The kappa value for each category, as well as the shared standard error, are computed and shown together with the overall kappa statistic.

Within the function, category-based vectors of counts were created from the original data.

```
> YES <- c(1,2,0,4,3,1,5,0,1,3)
> NO <- c(4,0,0,0,0,4,0,4,0,0)
> DONTKNOW <- c(0,3,5,1,2,0,0,1,4,2)
```

Then another function is called to do the final calculations.

```
> kap.ByCategory(category.counts =
  data.frame(YES,NO,DONTKNOW))
```

The result is omitted here since it is the same as above.

The function `kap.m.raters` is more often used because the data is easier to prepare. However, data.frame(YES,NO,DONTKNOW) has no information on the raters, yet will produce the same results. `kap.m.raters` thus, in fact, ignores raters, unlike `kap.2.raters`.

The **psy** package has a function called `lkappa` which gives quite similar results.

```
> lkappa(data.frame(rater1,rater2,rater3,rater4,rater5))
[1] 0.4588302
```

The resultant kappa statistic is not exactly the same as the one from **epicalc** because it uses a different formula.

kap.m.raters for 2 raters

Although the structure of the dataset for the function `kap.2.raters` and that for `kap.m.raters` are the same, the latter should not replace the former.

```
> kap.m.raters(data.frame(rater1, rater2))
Each category:
           kappa std.error    z p.value
yes        0.341     0.316 1.08   0.141
no         0.375     0.316 1.19   0.118
Don't know 0.608     0.316 1.92   0.027

Overall:
           kappa std.error    z p.value
           0.417     0.236 1.77   0.039

> kap.2.raters(rater1, rater2)

 Table for calculation of kappa
            rater2
rater1       yes no Don't know
  yes          5  2          1
  no           0  1          0
  Don't know   0  0          1

Observed agreement = 70 %
Expected agreement = 45 %
Kappa = 0.455
Standard error = 0.195 , Z = 2.336 , P value = 0.01
```

Note that the kappa statistic from the `kap.2.raters` function has a higher value than that from `kap.m.raters` because the former checks for agreement between the raters whereas the latter checks the distribution of rated scores on the individuals and ignores the source of the frequency counts in the output table. That is, the rater is ignored, as explained previously.

Summary

Examples of statistical methods for checking agreement include simple correlation, intra-class correlation (ICC) and the kappa statistic. Correlation is used to measure test-retest reliability. Low test-retest correlation will lead to regression dilution bias where the effect of exposure is under-estimated. The value of '$icc.agreement' resulting from the icc command measures the variance due to rated subjects compared to that due to raters. If it is high, there would be high agreement among the raters. The kappa statistic is used for categorical variables. Functions kap.2.raters and kap.table are appropriate when there are 2 raters. If the outcome has more than two categories, and it is ordinal, then choose an appropriate weighting scheme. If there are many raters, the function kap.m.raters can be used but must be interpreted with caution since it reflects the distribution of classification that individual rated subjects received rather than agreement that the raters gave.

Exercise

A doctor checks the agreement between fasting blood sugar measurements using blood collected from the ante-cubital vein and capillaries in the index finger. The results in mg/dl are stored in the following two vectors.

```
> venous     <- c(85, 138, 190,  92, 145, 223,  95, 108, 128,
  130)
> capillary  <- c(97, 149, 230, 108, 124, 180, 100, 120, 123,
  123)
```

Should the capillary blood test replace the venous blood test? Note that fasting blood sugar levels above 126 mg/dl are considered as diabetes mellitus.

Solutions to Exercises

Chapter 1

Problem 1

```
> p <- 0.3
> delta <- 0.05
> n <- 1.96^2*p*(1-p)/delta^2 ; n # 322.6944.
```

Thus 323 subjects are needed.

Problem 2

```
> p <- .05; delta <- .02
> n <- 1.96^2*p*(1-p)/delta^2 ; n # 456.19
```

Thus 457 subjects are needed.

Problem 3

```
> log(.01/(1-.01)) # -4.59512
> log(.1/(1-.1))   # -2.197225
> log(.5/(1-.5))   #  0
> log(.9/(1-.9))   #  2.197225
> log(1/(1-1))     #  Inf
```

Alternatively, one can create a vector consisting of the probabilities.

```
> p <- c(.01, .1, .5, .9, 1)
> log(p/(1-p))
[1] -4.5951 -2.1972  0.0000  2.1972     Inf
```

Note that in **R** the function `c` is used to combine values into a vector. You will discover that this function is very useful and is used throughout this book.

Chapter 2

Problem 1.

```
> sum(1:100*1:100)   # or sum((1:100)^2)
[1] 338350
```

Problem 2.

```
> x <- 1:1000
> x7 <- x[x/7==trunc(x/7)]  # or x7 <- x[x%%7==0]
> sum(x7)
[1] 71071
```

Problem 3.

```
> ht <- c(120,172,163,158,153,148,160,170,155,167)
> wt <- c(22,52,71,51,51,60,50,67,53,64)
> names <- c("Niece", "Son", "GrandPa", "Daughter", "Yai",
  "GrandMa", "Aunty", "Uncle", "Mom", "Dad")
> names(ht) <- names
> names(wt) <- names
> cbind(ht,wt)
> bmi <- wt/(ht/100)^2

> sort(bmi)
   Niece      Son   Aunty1 Daughter      Yai
15.27778 17.57707 19.53125 20.42942 21.78649
     Mom      Dad    Uncle  GrandPa  GrandMa
22.06035 22.94812 23.18339 26.72287 27.39226

> summary(bmi)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  15.28   19.76   21.92   21.69   23.12   27.39

> sd(bmi)
[1] 3.742951
```

In conclusion, 'Niece' has the lowest BMI at 15.27 kg/m^2 and 'GrandMa' has the highest BMI of 27.39 kg/m^2. The average of the BMI is 21.7 kg/m^2 and the standard deviation is 3.7 kg/m^2.

Chapter 3

Problem 1

There is more than one correct method.

First method

```
> a1 <- rbind(1:10, 11:20)
> a1
```

Second method

```
> a2 <- matrix(1:20, nr=2, byrow=TRUE)
> a2
```

Third method

```
> a2 <- t(cbind(1:10, 11:20))
> a2
```

Problem 2

```
> a1[,seq(from=1, to=10, by=2)]
```

Problem 3

```
> table1 <- cbind(c(15,30), c(20,22)); table1
> rownames(table1) <- c("Exposed","Non-exposed")
> colnames(table1) <- c("Diseased","Non-diseased")
> table1
> help(chisq.test)
> help(fisher.test)
> chisq.test(table1) # with Yates' continuity correction
> chisq.test(table1, correct=FALSE) # without
> fisher.test(table1) # default atlernative is "two.sided"
> fisher.test(table1, alternative="greater")
> fisher.test(table1, alternative="less")
```

Chapter 5

The choice of plot depends on the sample size and, to a lesser extent, what needs to be emphasized, such as understandability, discrimination between values or simply esthetics. It also depends on the consumers of the information who are the targets.

Values of individual elements on the scale	
Dotchart	The original values are all kept
Dotplot	Each value is forced to fall into one of the bins.
Box plot	Only the outlying values are displayed. Others are grouped into parts of the box.

Power to discriminate different values	
Dotchart	Discrimination power is high. Even a small difference can be noticed if the sample size is not large.
Dotplot	Since adjacent values are often forced into the same bin, the power of discrimination is lost.
Boxplot	Poor discrimination power as most of the dots disappear in the box.

Perception for frequency distribution of the values	
Dotchart	Empty space in the graph promptly conveys the information that there is no data in the area. Flat or slow rising indicates low frequency whereas sharp or steep rising indicates high frequency. Viewers must be educated to give proper interpretation.
Dotplot	Information on relative frequency is best conveyed by this graph. No need for education for interpretation.
Boxplot	The length of the box is counter-intuitive. Since the box is divided into two parts with more or less the same amount of data, a short part means high density and a long part means low density. Many people do not have this knowledge to interpret the result.

Information on sample size in each stratum	
Dotchart	Thickness of strata determined by the sample size.
Dotplot	Thickness of strata determined by the height of the most frequent bin, therefore, it can be visually distorted.
Boxplot	When 'varwidth=TRUE', as indicated in the command, the width of each box is determined by its sample size but not in linear proportion.

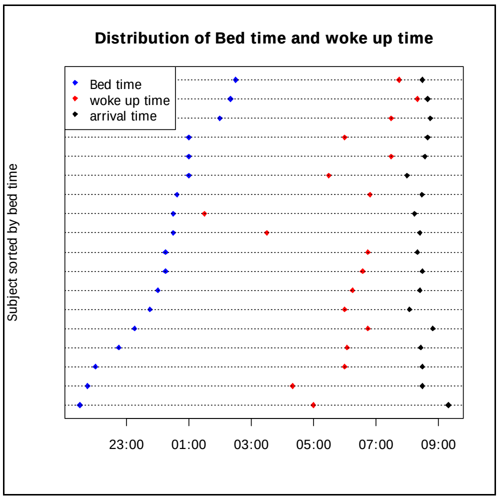
Missing values	
Dotchart	Missing values are placed as empty space on the top of each stratum
Dotplot	Missing values are not shown.
Boxplot	Missing values are not shown.

Suitability related to sample size and number of strata	
Dotchart	Most suitable when the sample size is not too large e.g. < 200. Large number of strata can be a problem, especially when the sample sizes among strata are grossly imbalanced.
Dotplot	Similar problem with '*summ*(var)' on the issue of stratification. However, 'dotplot' is more friendly when the sample size is large

Boxplot	Bearing only 5 values of a vector, this kind of graph is not burdened by a large sample size. In stratification analysis, sample sizes of strata are not proportional to the box width even if 'varwidth=TRUE' is imposed. Thus the graph can accommodate these problems quite well. On the other hand, length of the box may mislead the sample size as mentioned. Overall information on sample size is generally lacking on box plots. Median knot is introduced to indicate 95% confidence interval of the median. A smaller knot indicates a larger sample size or lower level of dispersion. However, the use of a knot is not popular.

Chapter 6

```
> zap()
> data(Timing)
> use(Timing)
> bed.day <- ifelse(bedhr > 20, 12, 13)
> bed.time <- ISOdatetime(year=2004, month=12, day=bed.day,
  hour=bedhr, min=bedmin, sec=0, tz="")
> woke.up.time <- ISOdatetime(year=2004, month=12, day=13,
  hour=wokhr, min=wokmin, sec=0, tz="")
> arrival.time <- ISOdatetime(year=2004, month=12, day=13,
  hour=arrhr, min=arrmin, sec=0, tz="")
> from.woke.to.work <- arrival.time - woke.up.time
> summ(from.woke.to.work)
> sortBy(bed.time)
> par(bg="cornsilk")
> plot(bed.time, 1:length(bed.time), xlim=c(min(bed.time),
  max(arrival.time)), pch=18, col="blue", ylab=" ", yaxt="n")
> points(woke.up.time, 1:length(woke.up.time), pch=18, col=2)
> points(arrival.time, 1:length(arrival.time), pch=18, col=1)
> abline(h=1:length(arrival.time), lty=3)
> title(main="Distribution of Bed time and woke up time")
```



```
> title(ylab="Subject sorted by bed time")
> legend("topleft", legend=c("Bed time", "woke up time",
  "arrival time"), pch=18, col=c("blue","red","black"),
  bg="cornsilk")
```

Chapter 7

No. As seen from

```
> addmargins(table(.data$onset, .data$case))
```

Three non-cases had reported onset time. The 'onset' that had been changed was the free vector created by the command

```
> onset[!case] <- NA
```

itself. In this command, both 'onset' and 'case' were those in the second position of the search path '`search()`', which was an *attached* copy of **`.data`**. From the command

```
> onset[!case] <- NA
```

there would be three copies of 'onset'. The first and the second one in **`.data`** and in 'search()[2]' which is not changed. These two copies are then different from the free vector which was created/modified by the command.

To get a permanent effect, the *`recode`* command in Epicalc should be used.

```
> recode(onset, !case, NA)
```

Then, check again:

```
> addmargins(table(.data$onset, .data$case))
```

By this method, the free vector 'onset' will be removed. The vectors in **`.data`** and in 'search()[2]' would also be automatically synchronised to the new value.

However, the variable 'time.onset', a *POSIXt* class object, does not have this problem. Using this variable in the **`.data`** in the next chapter would give no problem.

Chapter 8

Both 'beefcurry' and 'saltegg' have significant attributable risk and risk ratio. One might think that these foods would have been contaminated. In fact, the increase in risk from consumption of these is due to confounding. This is discussed in the next chapter.

Chapter 9

```
> cc(case, water) # OR =1.14, 95%CI = 0.47, 2.85
> table(case, eclair.eat, water)
```

Note one zero cell for a case who ate neither eclairs nor water. The following subsequent commands give MH odds ratio but not stratum specific OR and the homogeneity test results.

```
> mhor(case, eclair.eat, water)
  # MH OR = 24.3, 95% CI = 14.11, 41.7

> mhor(case, water, eclair.eat)
  # MH OR = 1.56, 95% CI =  0.60, 4.06
```

For stratification with beef curry, there is no problem with any cell with zero counts. The homogeneity test could be done without any serious problems.

```
> table(case, beefcurry, water)
> mhor(case, beefcurry, water)
```

Graphs cross, homogeneity test P value = 0.018

```
> mhor(case, water, beefcurry)
```

Graphs cross, homogeneity test P value = 0.016

Note the strong interaction of beef curry with eclair and with water, which needs a biological explanation.

Chapter 10

Solutions omitted.

Chapter 11

```
> des()
> plot(smoke, log(deaths))
> plot(SO2, log(deaths))
> plot(log(smoke), log(deaths))
> plot(log(SO2), log(deaths))
```

The last of the four plots looks the best.

```
> lm1 <- lm(log(deaths) ~ smoke)
> summary(lm1)$r.squared # 0.47
> lm2 <- lm(log(deaths) ~ SO2)
> summary(lm2)$r.squared # 0.59
> lm3 <- lm(log(deaths) ~ log(smoke))
> summary(lm3)$r.squared # 0.43
> lm4 <- lm(log(deaths) ~ log(SO2))
> summary(lm4)$r.squared # 0.66
```

The R-squared of 'lm4' is equal to the following model (using log base 2):

```
> lm5 <- lm(log2(deaths) ~ log2(SO2))
> summary(lm4)$r.squared # 0.66
```

The coefficients of log(SO2) from '`lm4`' and of log2(SO2) from '`lm5`' are the same: 0.45843.

For every unit increment of $\log_2$(SO2), the $\log_2$(deaths) increases by 0.458 units. Similarly, for every unit increment of $\log_e$(SO2), the $\log_e$(SO2) also increases by 0.458 units. This coefficient is thus independent of the base of logarithm. This means that the relationship between these two variables is on the power scale. Given *x* is a positive number, for every increment of SO2 by *x* times, the number of deaths will increase by $x^{0.45843}$ times.

```
> plot(log2(SO2), log2(deaths))
> abline(lm5)
```

From the regression coefficient and the graph, when the SO2 concentration in the air is doubled, the number of deaths will increase by $2^{0.45843}$ or 1.374 times. The modelling for outcome variable that is discrete counting number can be more appropriately dealt with Poisson regression in chapter 19.

Chapter 12

```
> zap()
> data(BP)
> use(BP)
> age.in.days <- as.Date("2001-03-12") - birthdate
> age <- as.numeric(age.in.days)/365.25
> sortBy(sbp)
> plot(sbp,ylim=c(0,max(sbp)),pch=" ",ylab="blood pressure")
> n <- length(sbp)
> segments(1:n, sbp, 1:n, dbp, col=unclass(sex))
> title(main="Systolic and diastolic blood pressure of the
  subjects")
> summary(lm(dbp ~ sex + age))
=======================
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  48.9647     9.4928   5.158 1.32e-06
sexfemale     7.2243     4.0798   1.771   0.0797
age           0.9412     0.1813   5.192 1.14e-06
=======================
```

After adjusting for age, the difference between sexes is not statistically significant.

Chapter 13

All the conclusions are independent of the base for logarithm and must be the same.

```
> log2money <- log2(money)
> summary(lm6 <- lm(log2money ~ age + age2))
==========================
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.340996   1.124481   0.303 0.769437
age          0.416419   0.058602   7.106 0.000101
age2        -0.004211   0.000668  -6.304 0.000232
---
> coef(lm6)
 (Intercept)          age         age2
 0.340996352  0.416418830 -0.004211267
> coef(lm4)
 (Intercept)          age         age2
 0.102650130  0.125354559 -0.001267718
> coef(lm4) / coef(lm6)
(Intercept)         age        age2
    0.30103     0.30103     0.30103
```

The unit in horizontal axis in model `lm4` is 30% that in `lm6`. The proportion is log 2 of base 10.

```
> log10(2)  # 0.30103
```

or the proportion between the two logarithms.

```
> log(2)/log(10)
```

In computing the expected age where money is carried in the maximum amount:

```
> a1 <- coef(lm6)[3]
> b1 <- coef(lm6) [2]
> c1 <- coef(lm6) [1]
> x1 <- -b1/(2*a1); x1   # 49.44104
> y1 <- a1 * x1^2 + b1 * x1 + c1
> y1; 2^y1  # 1590.304
```

Money carried is a maximum at the age of 49.4 and the estimate is 1590.3 baht. These results are the same as those from `lm4`, which uses logarithm base 10.

Chapter 14

The following commands are from a previous chapter.

```
> data(BP)
> use(BP)
> des()
> age.in.days <- as.Date("2001-03-12") - birthdate
> age <- as.numeric(age.in.days)/365.25
> saltadd1 <- saltadd
> levels(saltadd1) <- c("no", "yes", "missing")
> saltadd1[is.na(saltadd)] <- "missing"
```

These commands are specific for this chapter.

```
> glm1 <- glm(sbp ~ age * saltadd, family=gaussian)
> glm2 <- glm(sbp ~ age + saltadd, family=gaussian)
> glm3 <- glm(sbp ~ age, family=gaussian)
> glm1$aic
  [1] 781.1646

> glm2$aic
  [1] 780.535

> glm3$aic
  [1] 990.425
```

Of the three models, `glm2` has the lowest AIC. Of the three models it is therefore the best.

```
> summary(glm2)
===============
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  63.1291    15.7645   4.005 0.000142 ***
age           1.5526     0.3118   4.979 3.81e-06 ***
saltaddyes   22.9094     6.9340   3.304 0.001448 **
---
    Null deviance: 109757  on 79  degrees of freedom
Residual deviance:  73192  on 77  degrees of freedom
AIC: 780.53
```

Chapter 15

Problem 1

```
> use(complete.data)
> eclair.beefcurry <- eclair.eat + (beefcurry=="Yes")
> tab1(eclair.beefcurry)
> eclair.beefcurry <- factor(eclair.beefcurry)
> levels(eclair.beefcurry) <- c("none","either","both")
> pack()
> glm1 <- glm(case ~ eclair.beefcurry, binomial, data=.data)
> logistic.display(glm1)

Logistic regression predicting case

                         adj. OR(95%CI)      P(Wald's test) P(LR-test)
eclair.beefcurry: ref.="none":                              < 0.001
   either                0.79 (0.29,2.19)    0.651
   both                  11.88 (4.65,30.36)  < 0.001

Log-likelihood = -534.7787
No. of observations = 972
AIC value = 1075.5574
```

The model has only two terms related to eclair and beef curry. The last term contains the answer.

Problem 2

```
> zap()
> data(ANCtable); use(ANCtable)
> death <- factor(death, labels=c("no","yes"))
> anc <- factor(anc, labels=c("old","new"))
> clinic <- factor(clinic, labels=c("A","B"))
> data1 <- data.frame(death, anc, clinic, Freq)
> xtable <- xtabs(Freq~death+anc+clinic)
> mhor(mhtable=xtable)
Stratified analysis by  clinic
                OR lower lim. upper lim. P value
clinic A     0.801      0.346       1.90   0.556
clinic B     1.008      0.238       3.22   1.000
M-H combined 0.863      0.454       1.64   0.649

M-H Chi2(1) = 0.21 , P value = 0.649
Homogeneity test, chi-squared 1 d.f. = 0.11 , P value = 0.742
```

After stratifying by clinic, there is no difference in mortality between the two methods of ante-natal care.

Problem 3

```
> zap()
> data(Hakimi)
> use(Hakimi)
> treatment <- 2 - treatment
> table(treatment)
> label.var(treatment, "Treatment")
> cc(dead, treatment)

       treatment
dead      0   1 Total
  0     196 204   400
  1      28  37    65
  Total 224 241   465

OR =  1.269
95% CI = 0.725 2.242
Chi-squared = 0.786 ,  1 d.f. , P value = 0.375
Fisher's exact test (2-sided) P value = 0.423

> mhor(dead, treatment, malpres, graph=TRUE)
Stratified analysis by  malpres
                OR lower lim. upper lim. P value
malpres 0    0.672      0.335       1.32  0.2655
malpres 1    6.688      0.940      81.48  0.0386
M-H combined 0.911      0.514       1.62  0.7453

M-H Chi2(1) = 0.105 , P value = 0.745
Homogeneity test, chi-squared 1 d.f.=5.596, P value=0.018
```

The crude and adjusted odds ratios are different, however the homogeneity test is significant indicating that the strata specific odds ratios can not be combined. When 'malpres'=1, the effect of treatment on death is significant.

```
> summary(glm(dead ~ treatment, binomial) -> cox1)
> summary(glm(dead ~ treatment + malpres, binomial) -> cox2)
> summary(glm(dead ~ treatment*malpres, binomial) -> cox3)
> summary(glm(dead ~ treatment*malpres+birthwt*treatment,
  binomial) -> cox4)
> step(cox4)
```

We conclude that a significant interaction is evident between 'treatment' and 'malpres'. Birthweight is significant. The best model is found to be:

```
> m <- glm(dead ~ treatment*malpres+birthwt, family=binomial)
> logistic.display(m, decimal=1)

Logistic regression predicting dead

           crude OR(95%CI)     adj. OR(95%CI)      P(Wald)  P(LR-test)
treatment: 1.3 (0.7,2.2)       0.6 (0.3,1.1)       0.12     0.12
  1 vs 0

malpres:   13.2 (6.2,27.7)     1.6 (0.3,8.6)       0.6      0.61
  1 vs 0

birthwt    0.9985(0.998,0.999) 0.9986(0.998,0.999) < 0.001  < 0.001

treatment:malpres  -           14.4 (2,103.3)      0.01     0

Log-likelihood =  -154.5335
No. of observations =  465
AIC value = 319.07
```

Problem 4

```
> data(Ectopic)
> use(Ectopic)
> case <- outc == "EP"
> case <- factor(case)
> levels(case) <- c("control", "case")
> gravi1 <- unclass(gravi)
> m1 <- glm(case ~ hia + gravi1, family=binomial)
> logistic.display(m1, dec=1, crude=FALSE)

Logistic regression predicting case : case vs control

                         adj. OR(95%CI)    P(Wald test) P(LR-test)
hia: ever IA vs never IA 3.7 (2.5,5.4)     < 0.001      < 0.001

gravi1 (cont. var.)      1.0 (0.78,1.28)   1            1

Log-likelihood = -429.386
No. of observations = 723
AIC value = 864.773
```

There is no evidence of a linear dose-response relationship between gravidity and risk of ectopic pregnancy, after adjusting for 'hia'.

Chapter 16

Problem 1

```
> zap()
> library(survival)
> use(VC1to6)
> matchTab(case, alcohol, strata = matset)
===============
Odds ratio by Mantel-Haenszel method = 5.386

Odds ratio by maximum likelihood estimate (MLE) method = 5.655
 95%CI= 1.811 , 17.659

> clogit.display(clogit(case ~ alcohol + strata(matset)))
Call:
coxph(formula = Surv(rep(1, 119L), case) ~ alcohol +
  strata(matset), method = "exact")

  n= 119
        coef exp(coef) se(coef)    z      p
alcohol 1.73      5.66    0.581 2.98 0.0029

        exp(coef) exp(-coef) lower .95 upper .95
alcohol      5.66      0.177      1.81      17.7

Rsquare= 0.089   (max possible= 0.471 )
Likelihood ratio test= 11.1  on 1 df,   p=0.000843
Wald test            = 8.9  on 1 df,   p=0.00286
Score (logrank) test = 10.7  on 1 df,   p=0.00105
```

Problem 2

```
> clogit3 <- clogit(case ~ smoking + alcohol + rubber +
  strata(matset))
> clogit2 <- clogit(case ~ alcohol + rubber + strata(matset))
> clogit1 <- clogit(case ~ alcohol + strata(matset))
> clogit3$loglik
> clogit2$loglik
> clogit1$loglik
> clogit3
===============
Likelihood ratio test=12 on 3 df, p=0.00738 n=119
> clogit2
===============
Likelihood ratio test=11.5 on 2 df, p=0.00314 n=119
> clogit1
===============
Likelihood ratio test=11.1 on 1 df, p=0.000843 n=119
```

The conditional log likelihood and the likelihood ratio test of '`clogit1`', despite being the smallest among the three, has the lowest degrees of freedom. This model contains only 'alcohol', which is highly statistically significant whereas all other two independent variables are not. All of these facts suggest that '`clogit1`' should be the model of choice.

We can confirm this by using the likelihood ratio test:

```
> lrtest(clogit3, clogit2)
Likelihood ratio test for Cox regression & conditional
  logistic regression
Chi-squared 1 d.f. =  0.4743344 , P value =  0.491
```

Having one more degree of freedom with a small increase in likelihood is not worthwhile. Therefore, '`clogit2`' should be better than '`clogit3`'. The independent variable 'smoking' is now removed.

Similarly, we now test whether to keep 'rubber'.

```
> lrtest(clogit2, clogit1)
Likelihood ratio test for Cox regression & conditional
  logistic regression
Chi-squared 1 d.f. =  0.383735 , P value =  0.5356
```

Again, the models '`clogit2`' and '`clogit1`' are not statistically significant. The current choice should be '`clogit1`'. Drinking alcohol is the only significant predictor for oesophageal cancer.

Chapter 17

Set up the data:

```
> zap()
> outcome <- gl(n=3, k=4)
> levels(outcome) <- c("nochange","immuned","dead")
> vac <- gl(n=2, k=2, length= 12)
> levels(vac) <- c("placebo","vaccine")
> agegr <- gl(n=2, k=1, length=12)
> levels(agegr) <- c("young","old")
> total <- c(25,15,4,8,1,0,25,35,3,1,2,1)
> .data <- data.frame(outcome, vac, agegr, total)
> .data
```

Problem 1

```
> table1 <- xtabs(total ~ agegr+vac, data=.data)
> table1
> cc(cctable=table1) # OR = 2.552, P value = .023
```

Problem 2

```
> table2 <- xtabs(total~agegr+outcome, data=.data)
> table2
> fisher.test(table2) # p-value = 0.226
```

Problem 3

```
> table3 <- xtabs(total ~ outcome + vac, data=.data)
> table3
> fisher.test(table3) # p-value < 2.2e-16
> multi3 <- multinom(outcome ~ vac + agegr, weights=total,
  data=.data)
> s3 <- summary(multi3)
> mlogit.display(multi3) # AIC = 137.13
```

Recreate a model with age group removed.

```
> multi4 <- multinom(outcome ~ vac, weights=total, data=.data)
> s4 <- summary(multi4)
> mlogit.display(multi4) # AIC = 134.471
```

The model 'multi4' has a lower AIC than that of 'multi3'. Age group is therefore not appropriate to be in the model. From the last command, it is concluded that the vaccine increases the chance of getting immune with a highly significant odds ratio of 200. It should also be noted that the vaccine also (non-significantly) increases the chances of death.

Chapter 18

```
> zap()
> library(nnet)
> library(MASS)
> male <- c(rep(0, times=6), rep(1, times=6))
> drug <- rep(c(0,1), times=6)
> pain <- rep(1:3, times=4)
> total <- c(3,5,15,10,5,7,8,5,10,10,10,2)
```

For polytomous logistic regression:

```
> pain.cat <- factor(pain)
> levels(pain.cat) <- c("nill","mild","severe")
> pain.ord <- ordered(pain.cat)
> model.polytom <- multinom(pain.cat ~ drug + male,
  weights=total)
> summary(model.polytom)
> mlogit.display(model.polytom)
```

Shows a significant effect of drug in severe pain only. AIC = 191.623. For ordinal logistic regression:

```
> model.ord <- polr(pain.ord ~ drug + male, weights=total)
> summary(model.ord)
```

The AIC = 189.037, which is better (lower) than the polytomous model.

```
> ordinal.or.display(model.ord)
```

In conclusion, both drugs and being male have significant reduction on pain.

Chapter 19

The following model is run after setting up the variables using the commands in the text.

```
> model.pois <- step(glm(respdeath ~ agegr + period + arsenic2
  + start, offset=log(personyrs), family=poisson, data=.data))
> summary(model.pois)
> idr.display(model.pois)
```

Note that using 'arsenic2' in the model is better than using 'arsenic' suggesting no evidence of a dose-response relationship. Moreover, workers who started to work from 1925 had significantly lower risk than those who had started earlier.

```
> poisgof(model.pois)  # p.value = 0.40591
```

There is no evidence of overdispersion.

```
> model.nb <- glm.nb(respdeath ~ agegr + arsenic2 + start +
  offset(log(personyrs)), data=.data)
> summary(model.nb)  # theta = 49, S.E. = 107
```

Poisson regression could be used instead of negative binomial regression. Note that convergence problems occur if all variables are included in the negative binomial model, most likely due to the relatively small number of records.

Chapter 20

Problem 1

```
> model.bang1 <- glmmPQL(user ~ urban+ age_mean+
  living.children, random=~1 | district, binomial, data=.data)
> summary(model.bang1)
```

To compute the 95% confidence interval of odds ratios

```
> exp(intervals(model.bang1)$fixed)
```

Note that urban women have two times the odds of using contraceptives compared to rural women. A one year increment of age is associated with about a 3 percent reduction of odds of use.

Problem 2

From the last output, increasing the number of living children does not have a linear dose-response relationship with use. The odds almost doubles if the woman had two children and almost triples for women with three living children. However, as the number exceeds three, the odds of use does not further increase.

Problem 3

```
> model.bang2 <- glmmPQL(user ~ urban + age_mean +
  living.children, random = ~ age_mean | district,
  family=binomial, data=.data)
> logLik(model.bang1) # -4244.312 (df=8)
> logLik(model.bang2) # -4243.606 (df=10)
> lrtest(model.bang1, model.bang2) # P value=0.4933
```

Having age in the random effects is redundant.

Problem 4

```
> model.bang3 <- glmmPQL(user ~ urban * age_mean +
  living.children, random=~1 | district, family=binomial,
  data=.data)
> summary(model.bang3) # P value for interaction = 0.3887

> lrtest(model.bang1, model.bang3)
# Error:  Likelihood gets worse with more variables. Test not
  executed
```

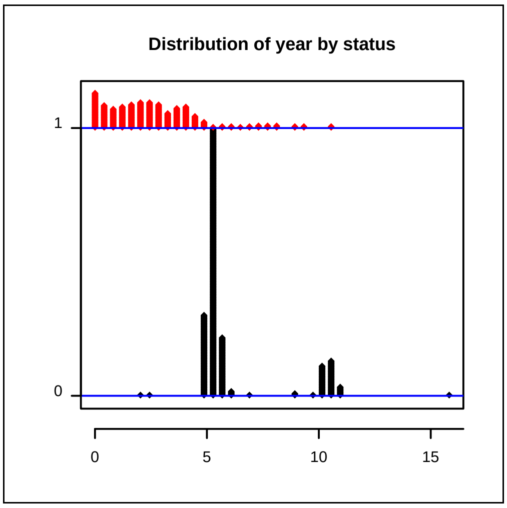
The evidence of age having a different effect in urban and rural areas is not found.

Chapter 21

```
> zap()
> data(Compaq)
> use(Compaq)
> des()
> summ()
```

Problem 1

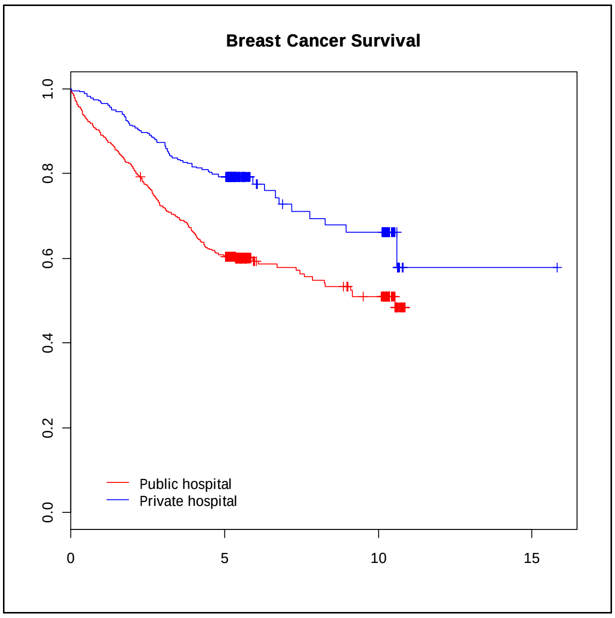
```
> summ(year, by = status)
> abline(v=c(5,6))
> dotplot(year, by=status)
```



Note that deaths are uniformly distributed in the first five years where there were only two censored observations. On the other hand, there was a lot censoring between the 5th and the 6th years where there were very few deaths. The second peak of censoring came after the 10th year. There is one patient who survived 15.8 years and was censored at the time the study ended. The alternating clustering of deaths and censoring would not be detected if the exploratory analysis was not done carefully.

Problem 2

```
> surv.ca <- Surv(year, status)
> plot(survfit(surv.ca ~ hospital), col = c("red", "blue"),
  legend.text = levels(hospital), main="Breast Cancer
  Survival")
```



Note the very dense censoring immediately after the 5th and the 10th years.

Problem 3

```
> survdiff(surv.ca ~ hospital)
> survdiff(surv.ca ~ hospital + strata(stage))
> survdiff(surv.ca ~ hospital + strata(agegr))
> survdiff(surv.ca ~ hospital + strata(ses))
```

The difference of survival between patients from the two types of the hospitals is highly significant despite the adjustments. Note that adjustment can only be done one variable at a time using this approach. Multivariate adjustment using Cox regression is presented in chapter 22.

Chapter 22

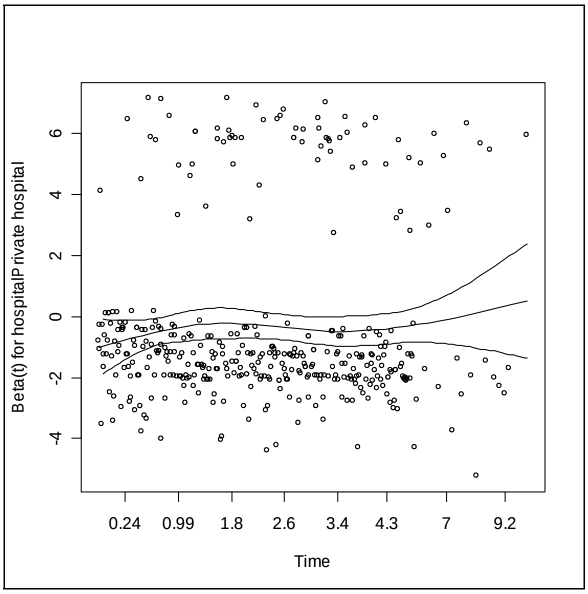
Problem 1

```
> coxph(surv.ca ~ hospital + stage + strata(ses) + agegr) ->
  model5
> cox.zph(model5)  # Global test p value = 0.00802
> coxph(surv.ca ~ hospital + stage + ses + strata(agegr)) ->
  model6
> cox.zph(model6)  # Global test p value = 0.00494
```

Models based on stratification by socio-economic status and by age still violate the proportional hazard assumption.

Problem 2

```
> plot(cox.zph(model4), var = 1)
```



The hazard ratio looks relative stable and slightly on the negative side for most of the time period. A notable feature of the graph is that there are two clusters of residuals. Some extreme positive values are sparsely found at the top of the plot whereas the majority lie in another cluster within 0 to -3 units of beta. This may suggest that the data actually came from more than one group of patients. Unfortunately, we could not further investigate this finding.

Chapter 23

Problem 1

```
> help(expsy)
> summ(expsy)
```

The items 'it1' to 'it10' all share the same rating scale (1: low to 4: high). The dataset is actually small enough to view on the screen

```
> expsy
```

Note the missing values.

```
> use(expsy)
> alpha(it1:it10)  # 4 items reversed
> alphaBest(it1:it10)$remaining -> wanted
> tableStack(vars=wanted, reverse=TRUE) -> b
```

Chapter 24

Problem 1

An estimate of the population prevalence is not known. However, we can obtain a range of sample sizes required corresponding to a range of values for p, say from 0.1 to 0.9.

```
> p <- seq(0.1,0.9,0.1)
> d <- 0.05
> n.for.survey(p, delta = d)

Sample size for survey.
Assumptions:
  Confidence limit = 95 %
  Delta            = 0.05 from the estimate.

    p delta   n
1 0.1  0.05 138
2 0.2  0.05 246
3 0.3  0.05 323
4 0.4  0.05 369
5 0.5  0.05 384
6 0.6  0.05 369
7 0.7  0.05 323
8 0.8  0.05 246
9 0.9  0.05 138
```

We see from the output above that the maximum sample size required is found when p is equal to 0.5. This is true for any survey where the estimated prevalence is not known beforehand and the precision is fixed. For these situations, the safest choice is to assume that p = 0.5.

Problem 2

```
> p2 <- 0.5; or <- 2
> odds2 <- p2/(1-p2)
> odds1 <- or*odds2
> p1 <- odds1/(1+odds1); p1
 [1] 0.6666667
> n.for.2p(p1,p2)
Estimation of sample size for testing Ho: p1==p2
Assumptions:
     alpha = 0.05
     power = 0.8
        p1 = 0.6666667
        p2 = 0.5
     n2/n1 = 1

Estimated required sample size:

        n1 = 148
        n2 = 148
   n1 + n2 = 296
```

Nearly 300 subjects are needed.

Problem 3

The worthwhile benefit is 2.5kg and since we don't know the actual means in the three groups, we can substitute any values for 'mu1' and 'mu2', so long as the difference is 2.5. Also, given that we are performing two comparisons, a reasonable type I error level (alpha) would be 0.02, instead of the conventional 0.05. The required sample sizes can then be obtained as follows:

```
> n.for.2means(mu1=10, mu2=12.5, sd1=3.5, sd2=3.5, ratio=2,
  alpha=0.02)

Estimation of sample size for testing Ho: mu1==mu2
====== assumptions omitted ======
Estimated required sample size:
        n1 = 31
        n2 = 61
   n1 + n2 = 92
```

Thus 61 controls are required, whereas 31 are each required in the two treatment groups, giving a total sample size required of 123. Note that if the standard deviations in each group are increased to 4.5kg, the required sample size is increased to 200.

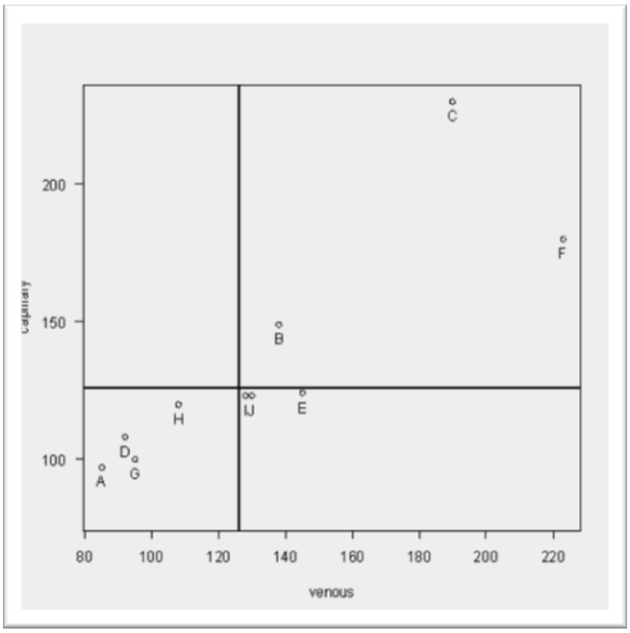
Chapter 29

Bland-Altman plot

```
> diff <- capillary-venous
> average <- (capillary + venous) / 2
> plot(average, diff)
> abline(h=0)
```

The differences vary around within +/- 20 mg/dl when the average not exceeding 150 mg/dl. When the levels are high, the differences vary by +/- 40 mg/dl, which is very high.

```
> plot(venous, capillary)
> text(venous, capillary, labels=LETTERS[1:10], pos=1)
> abline(h=126, v=126, lwd=2)
```



B, C and F are considered as diabetic by both methods. I, J and E have high venous blood sugar above 126 while not above this threshold by capillary methods. If venous blood is the gold standard, the test will be 3/6 or 50% (95% CI, from `ci.binomial(3,6)`, equals 12% to 88%). Specificity is 4/4 or 100% (95% CI = 40% to 100%).

The small dataset does not allow us to compute sensitivity and specificity with acceptable precision. In severe hyperglycemic cases, the capillary test may give a large different value from the venous blood. Therefore, it may not be suitable for drug adjustment.

Index

Epicalc Functions

addMissingRecords	Add missing records to a longitudinal data set
adjust	Adjusted and standardize mean, proportion and rate
aggregate.numeric	Compute summary statistics of a numeric variable
aggregate.plot	Plot summary statistics of a numeric variable by group
alpha, alphaBest	Cronbach's alpha
auc	Area under time-concentration curve
be2ad	Change year in B.E. to A.D.
cc	Odds ratio calculation and graphing
ci	Confidence interval of probability, mean and incidence
codebook	Codebook of a data frame
des	Desription of a data frame or a variable
detachAllData	Detach all data frames
dotplot	Dot plot
expand	Expand an aggregated data frame
fillin	Rectangularize a dataframe
followup.plot	Longitudinal followup plot
kap,…	Kappa statistics
keepData	Keep a subset of variables or records
label.var	Variable manipulation
lagVar	Create a vector of lagged or subsequent value
logistic.display	Tables for multivariate odds ratio, incidence density etc
lookup	Recode several values of a variable
lroc,…	ROC curve
lrtest	Likelihood ratio test
lsNoFunction	List non-function objects
markVisits	Mark visits of subjects in a long format
matchTab	Matched tabulation
mhor	Odds ratio calculation and graphing
n.for.2means,…	Sample size calculations
pack	Variable manipulation
poisgof	Goodness of fit test for modeling of count data
power.for.2means	Power calculation for two sample means and proportions
power.for.2p	Power calculation for two sample means and proportions
pyramid	Population pyramid
recode	Recode variable(s)
rename	Rename variable(s) in the default data frame
setTitle	Setting language of Epicalc graph title
shapiro.qqnorm	Normal Q-Q plots with Shapiro-Wilk's test
sortBy	Variable manipulation
summ	Summary with graph
tab1	One-way tabulation
tableStack	Tabulation of variables in a stack form
tabpct	Two-way tabulation
titleString	Replace commonly used words in Epicalc graph title

unclassDataframe	Unclass factor(s) in the default data frame
use	Quick command to read in data and attach
zap	Remove objects and detach all data frames

Epicalc Datasets

ANCdata	Dataset on effect of new antenatal care method on mortality
ANCtable	Dataset on effect of new ANC method on mortality (as a table)
Attitudes	Dataset from an attitude survey among hospital staff
BP	Dataset on blood pressure and determinants
Bang	Dataset from a Bangladesh fertility survey, 1988
Compaq	Dataset on cancer survival
DHF99	Dataset for exercise on predictors for mosquito larva infestation
Decay	Dataset on tooth decay and mutan streptococci
Ectopic	Dataset of a case-control study looking at history of abortion as a risk factor for ectopic pregnancy
Familydata	Dataset of a hypothetical family
HW93	Dataset from a study on hookworm prevalence and intensity
Hakimi	Dataset on effect of training personnel on neonatal mortality
IudAdmit	Dataset of admission of cases for IUD trials
Marryage	Dataset on age at marriage
Montana	Dataset on arsenic exposure and respiratory deaths
Oswego	Dataset from an outbreak of food poisoning in the US
Outbreak	Dataset from an outbreak of food poisoning on a sports day carnival, Thailand 1990.
Planning	Dataset for practicing cleaning, labelling and recoding
SO2	Dataset on air pollution and deaths in UK
Sleep3	Dataset on sleepiness in a workshop
Suwit	Hookworm infection and blood loss: SEAJTM 1970
Timing	Dataset on bed time, waking up and arrival at a workshop
VC1to1,	Datasets on a matched case-control study of esophageal cancer
Xerop	Dataset from an Indonesian study on vitamin A deficiency and risk of respiratory infection

About Epicalc

Open source and free software has been a mainstay for researchers, especially in the developing countries, where the need for computer software and the cost of some software applications has often been at odds. The increasing complexity of research projects and associated analytical requirements led to the development of **R** in the late 1990s. The current version of **R**, an open-source statistical software initially written by Robert Gentleman and Ross Ihaka of the Statistics Department of the University of Auckland, is the result of a collaborative effort involving contributions from all over the world. **R** provides a wide variety of statistical and graphical techniques, and is highly extensible.

The Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by UNICEF/UNDP/World Bank/WHO has supported the preparation of an **R** add-on package, Epicalc, to enable **R** to more easily deal with epidemiological data. Epicalc, written by Virasakdi Chongsuvivatwong of Prince of Songkla University, Hat Yai, Thailand, has been well accepted by members of the **R** core-team and the package is downloadable from CRAN (Comprehensive **R** Archive Network) <http://www.cran.r-project.org> which is mirrored by 69 academic institutes in 29 countries. Equally, Epicalc has been welcomed by students and users alike. On one hand, it assists data analysts in data exploration and management. On the other hand, it helps young epidemiologists to learn the key terms and concepts based on numerical and graphical results of the analysis.

Steven Wayling
Research Training Special Programme for Research and Training in Tropical Diseases (TDR)
World Health Organization
October, 2007