

Statistical Practice in Epidemiology

with 

Computer exercises

University of Tartu, Estonia

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Program

Daily timetable

9:00 – 9:30	Recap of yesterday's practicals
9:30 – 10:30	Lecture
10:30 – 11:00	Coffee break
11:00 – 13:00	Practical
13:00 – 14:00	Lunch
14:00 – 14:30	Recap of morning's practical
14:30 – 15:30	Lecture
15:30 – 16:00	Tea break
16:00 – 18:00	Practical

Friday 2 June – Day 1

8:30 – 9:00	Registration
9:00 – 9:15	Welcome (KF)
9:15 – 10:15	R History and Ecology
10:15 – 10:30	Data manipulation with <code>dplyr</code> (DG)
10:30 – 11:00	Coffee break
11:00 – 13:00	Practical—choose one: 1: Practice with basic R & Simple data input 2: Data manipulation with <code>dplyr</code>
13:00 – 14:00	Lunch
14:00 – 14:30	Recap of morning practical
14:30 – 15:30	Practical: Tabulation & base graphics (KF)
15:30 – 16:00	Tea break
16:00 – 16:30	Simple Poisson and binary regression (JP)
16:30 – 18:00	Practical: Incidence rates and proportions and their contrasts by <code>glm</code>
18:00 –	Welcome reception: at ??

Saturday 3 June – Day 2

9:00 – 9:30	Recap of yesterday's practicals.
9:30 – 10:00	Introduction to splines (MP)
10:00 – 10:45	Linear and generalized linear models (EL)
10:45 – 11:15	Coffee break
11:15 – 13:00	Practical: Linear regression & Poisson regression with estimation and reporting of linear and curved effects
13:00 – 14:00	Lunch
14:00 – 14:30	Recap of morning practical
14:30 – 15:30	Causal inference 1: basic concepts
15:30 – 16:00	Tea break
16:00 – 18:00	Practical: Causal inference

Sunday 4 June – Day 3

- 9:00 – 9:30 Recap of yesterday's practicals
- 9:30 – 10:30 More advanced graphics in R, including `ggplot2` (DG)
- 10:30 – 11:00 Coffee break.
- 11:00 – 13:00 Practical: Graphical meccano

Monday 5 June – Day 4

- 9:00 – 9:30 Recap of yesterday's practicals
- 9:30 – 10:30 Survival analysis: Kaplan Meier & basic Cox-model, and basic analysis of competing risks (JP)
- 10:30 – 11:00 Coffee break
- 11:00 – 13:00 Practical: Survival and competing risks in oral cancer
- 13:00 – 14:00 Lunch
- 14:00 – 14:30 Recap of morning practical
- 14:30 – 15:30 Dates in R; follow-up representation in `Lexis` objects, time-splitting, and SMR (BxC)
- 15:30 – 16:00 Tea break.
- 16:00 – 18:00 Practical: Time-splitting and SMR in Danish diabetes patients

Tuesday 6 June – Day 5

- 9:00 – 9:30 Recap of yesterday's practicals
- 9:30 – 10:30 Nested and matched cc-studies & Case-cohort studies (KF)
- 10:30 – 11:00 Coffee break.
- 11:00 – 13:00 Practical: CC study: Risk factors for coronary heart disease
- 13:00 – 14:00 Lunch
- 14:00 – 14:30 Recap of morning practical
- 14:30 – 15:30 Causal inference 2: model-based estimation of causal contrasts (EL)
- 15:30 – 16:00 Tea break.
- 16:00 – 18:00 Practical: Model-based estimation of causal contrasts (EL)
- 19:00 – Course dinner, venue TBA

Wednesday 7 June – Day 6

- 9:00 – 9:30 Recap of yesterday's practicals
- 9:30 – 10:30 Multistate models, Poisson models for rates and simulation of `Lexis` objects (BxC)
- 10:30 – 11:00 Coffee break.
- 11:00 – 12:15 Practical: Multistate-model: Renal complications
- 12:15 – 12:45 Recap of morning practical
- 12:45 – 13:00 Wrap-up and farewell.
- 13:00 – 14:00 Lunch

Further material will appear at this year's course website:

<http://bendixcarstensen.com/SPE>

Chapter 1

Exercises

Data sets

Datasets for the practicals in this course, as well as some useful Rscripts, will be available on the course homepage, in <https://spe-r.github.io/>. This is where you will also find the “housekeeping” scripts designed to save you typing.

To get all files in one go, download the zip file

<https://github.com/SPE-R/SPE/raw/gh-spe-material/SPE-all-material.zip>.

Graphical User Interfaces to R

When running the exercises it is a good idea to use a text editor instead of typing your commands directly at the R prompt. On Windows and macOS, R comes with a basic graphical user interface including a built-in text editor. Many people like to use the RStudio interface to R, which includes a very powerful syntax-highlighting editor.

Keyboard shortcuts

In the past we have found that some participants have had difficulty finding keys for symbols that are commonly used in the R language. In particular, the tilde symbol ~ is used in all modelling functions but not directly available on some keyboards. If this affects you then please consult the Wikipedia page: <http://en.wikipedia.org/wiki/Tilde#Keyboards> for advice on the combination of key presses you will need to get tilde.

Recaps

The R-scripts used during the course for the recaps will be available in <http://BendixCarstensen.com/SPE/recap>.

Ask for help

The faculty are here to help you. Ask them for help.

1.1 Practice with basic R

The main purpose of this session is to give participants who have not had much (or any) experience with using R a chance to practice the basics and to ask questions. For others, it should serve as a reminder of some of the basic features of the language.

R can be installed on all major platforms (*i.e.* Windows, macOS, Linux). We do not assume in this exercise that you are using any particular platform. Many people like to use the RStudio graphical user interface (GUI), which gives the same look and feel across all platforms.

1.1.1 The working directory

A key concept in R is the *working directory* (or *folder* in the terminology of Windows). The working directory is where R looks for data files that you may want to read in and where R will write out any files you create. It is a good idea to keep separate working directories for different projects. In this course we recommend that you keep a separate working directory for each exercise.

If you are working on the command line in a terminal, then you can change to the correct working directory and then launch R by typing “R”.

If you are using a GUI then you will typically need to change to the correct working directory after starting R. In RStudio, you can change directory from the “Session” menu. However it is much more useful to create a new *project* to keep your source files and data. When you open a project in the RStudio GUI, your working directory is automatically changed to the directory associated with the project.

You can quit R by typing

```
q()
```

at the R command prompt. You will be asked if you want to save your workspace. We recommend that you answer “no” to this question. If you answer “yes” then R will write a file named `.RData` into the working directory containing all the objects you created during your session so that they will be available next time you start R. This may seem convenient but you will soon find that your workspace becomes cluttered with old objects.

You can display the current working directory with the `getwd()` function and set it with the `setwd()` function. The function `dir()` can be used to see what files you have in the working directory.

1.1.2 Read-evaluate-print

The simplest use of R is interactively. R will read in the command you type, evaluate them, then print out the answer. This is called the *read-eval-print loop*, or REPL for people who don’t like words. In this exercise, we recommend that you work interactively. As the course evolves you will find that you need to switch to *script files*. We come back to this issue at the end of the exercise.

It is important to remember that R is case sensitive, so that `A` is different from `a`. Commands in R are generally separated by a newline, although a semi-colon can also be used.

1.1.3 Using R as a calculator

Try using R as a calculator by typing different arithmetic expressions on the command line. Note that R allows you to recall previous commands using the vertical arrow key. You can edit a recalled command and then resubmit it by pressing the return key. Keeping that in mind, try the following:

```
12+16
(12+16)*5
sqrt((12+16)*5) # square root
round(sqrt((12+16)*5),2) # round to two decimal places
```

The hash symbol # denotes the start of a *comment*. Anything after the hash is ignored by R.

Round braces are used a lot in R. In the above expressions, they are used in two different ways. Firstly, they can be used to establish the order of operations. In the example

```
> (12+16)*5
[1] 140
```

they ensure that 12 is added to 16 before the result is multiplied by 5. If you omit the braces then you get a different answer

```
> 12+16*5
[1] 92
```

because multiplication has higher *precedence* than addition. The second use of round braces is in a function call (e.g. `sqrt`, `round`). To call a function in R, type the name followed by the arguments inside round braces. Some functions take multiple arguments, and in this case they are separated by commas.

You can see that complicated expressions in R can have several levels of nested braces. To keep track of these, it helps to use a syntax-highlighting editor. For example, in RStudio, when you type an opening bracket “(”, RStudio will automatically add a closing bracket “)”, and when the cursor moves past a closing bracket, RStudio will automatically highlight the corresponding opening bracket (in grey). Features like this can make it much easier to write R code free from syntax errors.

Instead of printing the result you can store it in an object, say

```
a <- round(sqrt((12+16)*5),2)
```

In this case R does not print anything to the screen. You can see the results of the calculation, stored in the object `a`, by typing `a` and also use `a` for further calculations, e.g:

```
exp(a)
log(a)      # natural logarithm
log10(a)    # log to the base 10
```

The left arrow expression `<-`, pronounced “gets”, is called the assignment operator, and is obtained by typing `<` followed by `-` (with no space in between). It is also possible to use the equals sign `=` for assignment. Note that some R experts do not like this and recommend to use only “gets” for assignment, reserving `=` for function arguments,

You can also use a right arrow, as in

```
round(sqrt((12+16)*5),2) -> a
```

1.1.4 Vectors

All commands in R are *functions* which act on *objects*. One important kind of object is a *vector*, which is an ordered collection of numbers, or character strings (e.g. “Charles Darwin”), or logical values (TRUE or FALSE). The components of a vector must be of the same type (numeric, character, or logical). The combine function `c()`, together with the assignment operator, is used to create vectors. Thus

```
> v <- c(4, 6, 1, 2.2)
```

creates a vector `v` with components 4, 6, 1, 2.2 and assigns the result to the vector `v`.

A key feature of the R language is that many operations are *vectorized*, meaning that you can carry out the same operation on each element of a vector in a single operation. Try

```
> v
> 3+v
> 3*v
```

and you will see that R understands what to do in each case.

R extends ordinary arithmetic with the concept of a *missing value* represented by the symbol `NA` (Not Available). Any operation on a missing value creates another missing value. You can see this by repeating the same operations on a vector containing a missing value:

```
> v <- c(4, 6, NA)
> 3 + v
> 3 * v
```

The fact that every operation on a missing value produces a missing value can be a nuisance when you want to create a summary statistic for a vector:

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

While it is true that the mean of `v` is unknown because the value of the third element is missing, we normally want the mean of the non-missing elements. Fortunately the `mean` function has an optional argument called `na.rm` which can be used for this.

```
> mean(v, na.rm=TRUE)
[1] 5
```

Many functions in R have optional arguments that can be omitted, in which case they take their default value (in this case `na.rm=FALSE`), or can be explicitly given in the function call to override the default behaviour.

You can get a description of the structure of any object using the function `str()`. For example, `str(v)` shows that `v` is numeric with 4 components. If you just want to know the length of a vector then it is much easier to use the `length` function.

```
> length(v)
```


1.1.5 Sequences

There are short-cut functions for creating vectors with a regular structure. For example, if you want a vector containing the sequence of integers from 1 to 10, you can use

```
> 1:10
```

The `seq()` function allows the creation of more general sequences. For example, the vector (15, 20, 25, ... ,85) can be created with

```
> seq(from=15, to=85, by=5)
```

The objects created by the “:” operator and the `seq()` function are ordinary vectors, and can be combined with other vectors using the combine function:

```
> c(5, seq(from=20, to=85, by=5))
```

You can learn more about functions by typing `?` followed by the function name. For example `?seq` gives information about the syntax and usage of the function `seq()`.

1. Create a vector `w` with components 1, -1, 2, -2
2. Display this vector
3. Obtain a description of `w` using `str()`
4. Create the vector `w+1`, and display it.
5. Create the vector `v` with components (5, 10, 15, ... , 75) using `seq()`.
6. Now add the components 0 and 1 to the beginning of `v` using `c()`.
7. Find the length of this vector.

1.1.6 Displaying and changing parts of a vector (indexing)

Square brackets in R are used to extract parts of vectors. So `x[1]` gives the first element of vector `x`. Since R is vectorized you can also supply a vector of integer index values inside the square brackets. Any expression that creates an integer vector will work.

Try the following commands:

```
> x <- c(2, 7, 0, 9, 10, 23, 11, 4, 7, 8, 6, 0)
> x[4]
> x[3:5]
> x[c(1,5,8)]
> x[(1:6)*2]
> x[-1]
```

Negative subscripts mean “drop this element”. So `x[-1]` returns every element of `x` except the first.

Trying to extract an element that is beyond the end of the vector is, surprisingly, not an error. Instead, this returns a missing value

```
> N <- length(x)
> x[N + 1]
[1] NA
```

There is a reason for this behaviour, which we will discuss in the recap.

R also allows *logical subscripting*. Try the following

```
> x > 10
> x[x > 10]
```

The first expression creates a logical vector of the same length as **x**, where each element has the value **TRUE** or **FALSE** depending on whether or not the corresponding element of **x** is greater than 10. If you supply a logical vector as an index, R selects only those elements for which the condition is **TRUE**.

You can combine two logical vectors with the operators **&** (“logical and”) and **|** (“logical or”). For example, to select elements of **x** that are between 10 and 20 we combine two one-sided logical conditions for $x \geq 10$ **and** $x \leq 20$:

```
> x[x >= 10 & x <= 20]
```

The remaining elements of **x** that are **either** less than 10 **or** greater than 20 are selected with

```
> x[x < 10 | x > 20]
```

Indexing can also be used to replace parts of a vector:

```
> x[1] <- 1000
> x
```

This replaces the first element of **x**. Logical subscripting is useful for replacing parts of a vector that satisfy a certain condition. For example to replace all elements that take the value 0 with the value 1:

```
> x[x==0] <- 1
> x
```

If you want to replace parts of a vector then you need to make sure that the replacement value is either a single value, as in the example above, or a vector equal in length to the number of elements to be replaced. For example, to replace elements 2, 3, and 4 we need to supply a vector of replacement values of length 3.

```
> x[2:4] <- c(0, 8, 1)
> x
```

It is important to remember this when you are using logical subscripting because the number of elements to be replaced is not given explicitly in the R code, and it is easy to get confused about how many values need to be replaced. If we want to add 3 to every element that is less than 3 then we can break the operation down into 3 steps:

```
> y <- x[x < 3]
> y <- y + 3
> x[x < 3] <- y
> x
```

First we extract the values to be modified, then we modify them, then we write back the modified values to the original positions. R experts will normally do this in a single expression.

```
> x[x < 3] <- x[x < 3] + 3
```

Remember, if you are confused by a complicated expression you can usually break it down into simpler steps.

If you want to create an entirely new vector based on some logical condition then use the `ifelse()` function. This function takes three arguments: the first is a logical vector; the second is the value taken by elements of the logical vector that are `TRUE`; and the third is the value taken by elements that are `FALSE`.

In this example, we use the remainder operator `%%` to identify elements of `x` that have value 0 when divided by 2 (i.e. the even numbers) and then create a new character vector with the labels “even” and “odd”:

```
> x %% 2
> ifelse(x %% 2 == 0, "even", "odd")
```

Now try the following:

8. Display elements that are less than 10, but greater than 4
9. Modify the vector `x`, replacing by 10 all values that are greater than 10
10. Modify the vector `x`, multiplying by 2 all elements that are smaller than 5 (Remember you can do this in steps).

1.1.7 Lists

Collections of components of different types are called *lists*, and are created with the `list()` function. Thus

```
> m <- list(4, TRUE, "name of company")
> m
```

creates a list with 3 components: the first is numeric, the second is logical and the third is character. A list element can be any object, including another list. This flexibility means that functions that need to return a lot of complex information, such as statistical modelling functions, often return a list.

As with vectors, single square brackets are used to take a subset of a list, but the result will always be another list, even if you select only one element

```
> m[1:2] #A list containing first two elements of m
> m[3]   #A list containing the third element of m
```

If you just want to extract a single element of a list then you must use double square braces:

```
> m[[3]] #Extract third element
```

Lists are more useful when their elements are named. You can name an element by using the syntax `name=value` in the call to the `list` function:

```
> mylist <- list(name=c("Joe", "Ann", "Jack", "Tom"),
+               age=c(34, 50, 27, 42))
> mylist
```

This creates a new list with the elements “name”, a character vector of names, and “age” a numeric vector of ages. The components of the list can be extracted with a dollar sign `$`

```
> mylist$name
> mylist$age
```

1.1.8 Data frames

Data frames are a special structure used when we want to store several vectors of the same length, and corresponding elements of each vector refer to the same record. For example, here we create a simple data frame containing the names of some individuals along with their age in years, their sex (coded 1 or 2) and their height in cm.

```
> mydata <- data.frame(name=c("Joe", "Ann", "Jack", "Tom"),
+                       age=c(34, 50, 27, 42), sex=c(1, 2, 1, 1),
+                       height=c(185, 170, 175, 182))
```

The construction of a data frame is just like a named list (except that we use the constructor function `data.frame` instead of `list`). In fact data frames are lists so, for example, you can extract vectors using the dollar sign or other extraction methods for lists:

```
> mydata$height
> mydata[[4]]
```

On the other hand, data frames are also two dimensional objects:

```
> mydata
  name age sex height
1  Joe  34   1    185
2  Ann  50   2    170
3 Jack  27   1    175
4  Tom  42   1    182
```

When you print a data frame, each variable appears in a separate column. You can use square brackets with two comma-separated arguments to take subsets of rows or columns.

```
> mydata[1,]
> mydata[,c("age", "height")]
> mydata[2,4]
```

We will look into indexing of data frames in more detail below.

Now let's create another data frame with more individuals than the first one:

```
> yourdata <- data.frame(name=c("Ann", "Peter", "Sue", "Jack", "Tom", "Joe", "Jane"),
+                       weight=c(67, 81, 56, 90, 72, 79, 69))
```

This new data frame contains the weights of the individuals. The two data sets can be joined together with the `merge` function.

```
> newdata <- merge(mydata, yourdata)
> newdata
```

The `merge` function uses the variables common to both data frames – in this case the variable “name” – to uniquely identify each row. By default, only rows that are in both data frames are preserved, the rest are discarded. In the above example, the records for Peter, Sue, and Jane, which are not in `mydata` are discarded. If you want to keep them, use the optional argument `all=TRUE`.

```
> newdata <- merge(mydata, yourdata, all=TRUE)
> newdata
```

This keeps a row for all individuals but since Peter, Sue and Jane have no recorded age, height, or sex these are missing values.

1.1.9 Working with built-in data frames

We shall use the `births` data which concern 500 mothers who had singleton births (i.e. no twins) in a large London hospital. The outcome of interest is the birth weight of the baby, also dichotomised as normal or low birth weight. These data are available in the `Epi` package:

```
> library(Epi)
> data(births)
> objects()
```

The function `objects()` shows what is in your workspace. To find out a bit more about `births` try

```
help(births)
```

11. The dataframe "`diet`" in the `Epi` package contains data from a follow-up study with coronary heart disease as the end-point. Load these data with

```
> data(diet)
```

and print the contents of the data frame to the screen..

12. Check that you now have two objects, `births`, and `diet` in your workspace.
13. Get help on the object `diet`.
14. Remove the object `diet` with the command

```
> remove(diet)
```

Check that the object `diet` is no longer in your workspace.

1.1.10 Referencing parts of the data frame (indexing)

Typing `births` will list the entire data frame – not usually very helpful. You can use the `head` function to see just the first few rows of a data frame

```
> head(births)
```

Now try

```
> births[1,"bweight"]
```

This will list the value taken by the first subject for the `bweight` variable. Alternatively

```
> births[1,2]
```

will list the value taken by the first subject for the second variable (which is `bweight`). Similarly

```
> births[2,"bweight"]
```

will list the value taken by the second subject for `bweight`, and so on. To list the data for the first 10 subject for the `bweight` variable, try

```
> births[1:10, "bweight"]
```

and to list all the data for this variable, try

```
> births[, "bweight"]
```

To list the data for the first subject try

```
> births[1, ]
```

An empty index before the comma means “all rows” and an empty index after the comma means “all columns”.

15. Display the data on the variable `gestwks` for row 7 in the `births` data frame.

16. Display all the data in row 7.

17. Display the first 10 rows for the variable `gestwks`.

The `subset` function is another way of getting subsets from a data frame. To select all subjects with height less than 180 cm from the data frame `mydata` we use

```
> subset(mydata, height < 180)
```

The `subset` function is usually clearer than the equivalent code using `[]`:

```
> mydata[mydata$height < 180, ]
```

Another advantage of `subset` is that it will drop observations with missing values. Compare the following

```
> newdata[newdata$height < 180, ]
> subset(newdata, height < 180)
```

If `height` is missing then `subset` will drop that row. But `[]` will do something you might not expect. It will include the rows with missing `height`, but will replace every element in those rows with the missing value `NA`.

1.1.11 Summaries

A good way to start an analysis is to ask for a summary of the data by typing

```
> summary(births)
```

This prints some summary statistics (minimum, lower quartile, mean, median, upper quartile, maximum). For variables with missing values, the number of `NA`s is also printed.

To see the names of the variables in the data frame try

```
> names(births)
```

Variables in a data frame can be referred to by name, but to do so it is necessary also to specify the name of the data frame. Thus `births$hyp` refers to the variable `hyp` in the `births` data frame, and typing `births$hyp` will print the data on this variable. To summarize the variable `hyp` try

```
> summary(births$hyp)
```

Alternatively you can use

```
> with(births, summary(hyp))
```

1.1.12 Generating new variables

New variables can be produced using assignment together with the usual mathematical operations and functions. For example

```
> logbw <- log(births$bweight)
```

produces the variable `logbw` in your workspace, while

```
> births$logbw <- log(births$bweight)
```

produces the variable `logbw` in the `births` data frame.

You can also replace existing variables. For example `bweight` measures birth weight in grams. To convert the units to kilograms we replace the original variable with a new one:

```
> births$bweight <- births$bweight/1000
```

1.1.13 Turning a variable into a factor

In R categorical variables are known as *factors*, and the different categories are called the *levels* of the factor. Variables such as `hyp` and `sex` are originally coded using integer codes, and by default R will interpret these codes as numeric values taken by the variables. Factors will become very important later in the course when we study modelling functions, where factors and numeric variables are treated very differently. For the moment, you can think of factors as “value labels” that are more informative than numeric codes.

For R to recognize that the codes refer to categories it is necessary to convert the variables to be factors, and to label the levels. To convert the variable `hyp` to be a factor, try

```
> births$hyp <- factor(births$hyp, labels=c("normal", "hyper"))
```

This takes the original numeric codes (0, 1) and replaces them with informative labels “normal” and “hyper” for normal blood pressure and hypertension, respectively.

18. Convert the variable `sex` into a factor with labels “M” and “F” for values 1 and 2, respectively

1.1.14 Frequency tables

When starting to look at any new data frame the first step is to check that the values of the variables make sense and correspond to the codes defined in the coding schedule. For categorical variables (factors) this can be done by looking at one-way frequency tables and checking that only the specified codes (levels) occur. The most useful function for making simple frequency tables is `table`. The distribution of the factor `hyp` can be viewed using

```
> with(births, table(hyp))
```

or by specifying the data frame as in

```
> table(births$hyp)
```

For simple expressions the choice is a matter of taste, but `with` is shorter for more complicated expressions.

19. Find the frequency distribution of **sex**.
20. If you give two or more arguments to the **table** function then it produces cross-tabulations. Find the two-way frequency distribution of **sex** and **hyp**.
21. Create a logical variable called **early** according to whether **gestwks** is less than 30 or not. Make a frequency table of **early**.

1.1.15 Grouping the values of a numeric variable

For a numeric variable like **matage** it is often useful to group the values and to create a new factor which codes the groups. For example we might cut the values taken by **matage** into the groups 20–29, 30–34, 35–39, 40–44, and then create a factor called **agegrp** with 4 levels corresponding to the four groups. The best way of doing this is with the function **cut**. Try

```
> births$agegrp <- cut(births$matage, breaks=c(20,30,35,40,45), right=FALSE)
> with(births, table(agegrp))
```

By default the factor levels are labelled [20-25), [25-30), etc., where [20-25) refers to the interval which includes the left hand end (20) but not the right hand end (25). This is the reason for **right=FALSE**. When **right=TRUE** (which is the default) the intervals include the right hand end but not the left hand.

Observations which are not inside the range specified by the **breaks** argument result in missing values for the new factor. Hence it is important that the first element in **breaks** is smaller than the smallest value in your data, and the last element is larger than the largest value.

22. Summarize the numeric variable **gestwks**, which records the length of gestation for the baby, and make a note of the range of values.
23. Create a new factor **gest4** which cuts **gestwks** at 20, 35, 37, 39, and 45 weeks, including the left hand end, but not the right hand. Make a table of the frequencies for the four levels of **gest4**.

1.1.16 Saving and loading data

As noted in section 1.1.1, at the end of the session, R will offer to save your workspace and, if you accept, it will create a file **.RData** in your working directory. In fact you can save any R object to disc. For example, to save the data frame **births** try

```
> save(births, file="births.RData")
```

which will save the **births** data frame in the file **births.RData**. If you send this file to a colleague then they can read the data back into R with

```
> load("births.RData")
```

The commands **save()** and **load()** can be used with any R objects, but they are particularly useful when dealing with large data frames. The binary format created by the **save()** functions is the same across all platforms and between R versions.

1.1.17 The search path

When you load a package with the `library()` function, the functions in that package become available for you to use via a mechanism called the *search path*. The command

```
> search()
```

shows the positions on the search path. The first position is “.GlobalEnv”. This is the global environment, which is another name for your workspace. The second entry on the search path is the Epi package, the third is a package of commands called methods, the fourth is a package called stats, and so on. To see what is in the workspace try

```
> objects()
```

You should see the objects that you have created in this session. To see what is in the Epi package, try

```
> objects(2)
```

You can also refer to a package by name, not position

```
> objects("package:Epi")
```

When you type the name of an object R looks for it in the order of the search path and will return the first object with this name that it finds.

1.1.18 Attaching a data frame

The search path can also be modified by attaching a data frame. For example:

```
> attach(births)
```

This places a copy of the variables in the `births` data frame in position 2 of the search path. You can verify this with

```
> search()
> objects(2)
```

which shows the objects in this position are the variables from the `births` data frame.

Attaching a data frame makes the variables in it directly accessible. For example, when you type the command:

```
> hyp
```

you should get the variable `hyp` from the `births` data set without having to use the dollar sign. The `detach()` function removes the data frame from the search path.

```
> detach()
```

when no arguments are given, the `detach()` function removes the second entry on the search path (after the global environment).

This seems like an attractive feature, especially for people who are used to other statistical software (e.g. SAS, Stata) in which the variables in the “current working dataset” are directly accessible in this way. However, attaching data frames causes more problems than it solves and should be avoided. In particular:

- Since the attached data frame appears second in the search path, it comes after the global environment. If you have an object `hyp` in the global environment then you will get this, instead of the variable from the `births` data frame. This is called *masking*. R will warn you about masking, but only once for each variable.
- Attaching a data frame creates a copy of all the variables in it. Subsequent changes to the data frame (e.g. selecting rows or recoding variables) are not reflected in the attached copy, which is a snapshot of the data frame when it was attached.
- If you forget to `detach()` the data frame when you are finished with it, then you may create multiple attached copies on your search path, especially when using a script.

It is best to stick to using the dollar sign to select variables in a data frame, or to use the `with()` function. Many R functions (but not all of them) have a `data` argument which can be used to specify a data frame that should be searched before the search path.

1.1.19 Interactive use vs scripting

You can work with R simply by typing function calls at the command prompt and reading the results as they are printed. This is OK for simple use but rapidly becomes cumbersome. If the results of one calculation are used to feed into the next calculation, it can be difficult to go back if you find you have made a mistake, or if you want to repeat the same commands with different data.

When working with R it is best to use a text editor to prepare a batch file (or script) which contains R commands and then to run them from the script. If you are using a GUI then you can use the built-in script editor, or you can use your favourite text editor instead if you prefer.

One major advantage of running all your R commands from a script is that you end up with a record of exactly what you did which can be repeated at any time. This will also help you redo the analysis in the (highly likely) event that your data changes before you have finished all analyses.

1.2 Reading data into R

1.2.1 Introduction

“If you want to have rabbit stew, first catch the rabbit” – Old saying, origin unknown

R is a language and environment for data analysis. If you want to do something interesting with it, you need data.

For teaching purposes, data sets are often embedded in R packages. The base R distribution contains a whole package dedicated to data which includes around 100 data sets. This is attached towards the end of the search path, and you can see its contents with

```
> objects("package:datasets")
```

A description of all of these objects is available using the `help()` function. For example

```
> help(Titanic)
```

gives an explanation of the `Titanic` data set, along with references giving the source of the data.

The `Epi` package also contains some data sets. These are not available automatically when you load the `Epi` package, but you can make a copy in your workspace using the `data()` function. For example

```
> library(Epi)
> data(bdendo)
```

will create a data frame called `bdendo` in your workspace containing data from a case-control study of endometrial cancer. Datasets in the `Epi` package also have help pages: type `help(bdendo)` for further information.

To go back to the cooking analogy, these data sets are the equivalent of microwave ready meals, carefully packaged and requiring minimal work by the consumer. Your own data will never be able in this form and you must work harder to read it in to R.

This exercise introduces you to the basics of reading external data into R. It consists of reading the same data from different formats. Although this may appear repetitive, it allows you to see the many options available to you, and should allow you to recognize when things go wrong.

getting the data: You will need to download the zip file `data.zip` from the course web site <https://spe-r.github.io/data.zip> and unpack this in your working directory. This will create a sub-directory `data` containing (among other things) the files `fem.dat`, `fem-dot.dat`, `fem.csv`, and `fem.dta` (Reminder: use `setwd()` to set your working directory).

1.2.2 Data sources

Sources of data can be classified into three groups:

1. Data in human readable form, which can be inspected with a text editor.

2. Data in binary format, which can only be read by a program that understands that format (SAS, SPSS, Stata, Excel, ...).
3. Online data from a database management system (DBMS)

This exercise will deal with the first two forms of data. Epidemiological data sets are rarely large enough to justify being kept in a DBMS. If you want further details on this topic, you can consult the “R Data Import/Export” manual that comes with R.

1.2.3 Data in text files

Human-readable data files are generally kept in a rectangular format, with individual records in single rows and variables in columns. Such data can be read into a data frame in R.

Before reading in the data, you should inspect the file in a text editor and ask three questions:

1. How are columns in the table separated?
2. How are missing values represented?
3. Are variable names included in the file?

The file `fem.dat` contains data on 118 female psychiatric patients. The data set contains nine variables.

ID	Patient identifier
AGE	Age in years
IQ	Intelligence Quotient (IQ) score
ANXIETY	Anxiety (1=none, 2=mild, 3=moderate, 4=severe)
DEPRESS	Depression (1=none, 2=mild, 3=moderate or severe)
SLEEP	Sleeping normally (1=yes, 2=no)
SEX	Lost interest in sex (1=yes, 2=no)
LIFE	Considered suicide (1=yes, 2=no)
WEIGHT	Weight change (kg) in previous 6 months

Inspect the file `fem.dat` with a text editor to answer the questions above.

The most general function for reading in free-format data is `read.table()`. This function reads a text file and returns a data frame. It tries to guess the correct format of each variable in the data frame (integer, double precision, or text).

Read in the table with:

```
> fem <- read.table("./data/fem.dat", header=TRUE)
```

Note that you must assign the result of `read.table()` to an object. If this is not done, the data frame will be printed to the screen and then lost.

You can see the names of the variables with

```
> names(fem)
```

The structure of the data frame can be seen with

```
> str(fem)
```

You can also inspect the top few rows with

```
> head(fem)
```

Note that the IQ of subject 9 is -99, which is an illegal value: nobody can have a negative IQ. In fact -99 has been used in this file to represent a missing value. In R the special value NA (“Not Available”) is used to represent missing values. All R functions recognize NA values and will handle them appropriately, although sometimes the appropriate response is to stop the calculation with an error message.

You can recode the missing values with

```
> fem$IQ[fem$IQ == -99] <- NA
```

Of course it is much better to handle special missing value codes when reading in the data. This can be done with the `na.strings` argument of the `read.table()` function. See below.

1.2.4 Things that can go wrong

Sooner or later when reading data into R, you will make a mistake. The frustrating part of reading data into R is that most mistakes are not fatal: they simply cause the function to return a data frame that is *not what you wanted*. There are three common mistakes, which you should learn to recognize.

1.2.4.1 Forgetting the headers

The first row of the file `fem.dat` contains the variable names. The `read.table()` function does not assume this by default so you have to specify this with the argument `header=TRUE`. See what happens when you forget to include this option:

```
> fem2 <- read.table("data/fem.dat")
> str(fem2)
> head(fem2)
```

and compare the resulting data frame with `fem`. What are the names of the variables in the data frame? What is the class of the variables?

Explanation: Remember that `read.table()` tries to guess the mode of the variables in the text file. Without the `header=TRUE` option it reads the first row, containing the variable names, as data, and guesses that all the variables are character, not numeric. By default, all character variables are coerced to factors by `read.table`. The result is a data frame consisting entirely of factors. (You can prevent the conversion of character variables to factors with the argument `as.is=TRUE`).

If the variable names are not specified in the file, then they are given default names `V1`, `V2`, You will soon realise this mistake if you try to access a variable in the data frame by, for example

```
> fem2$IQ
```

as the variable will not exist

There is one case where omitting the `header=TRUE` option is harmless (apart from the situation where there is no header line, obviously). When the first row of the file contains **one less** value than subsequent lines, `read.table()` infers that the first row contains the variable names, and the first column of every subsequent row contains its **row name**.

1.2.4.2 Using the wrong separator

By default, `read.table` assumes that data values are separated by any amount of white space. Other possibilities can be specified using the `sep` argument. See what happens when you assume the wrong separator, in this case a tab, which is specified using the escape sequence `"\t"`

```
> fem3 <- read.table("data/fem.dat", sep="\t")
> str(fem3)
```

How many variables are there in the data set?

Explanation: If you mis-specify the separator, `read.table()` reads the whole line as a single character variable. Once again, character variables are coerced to factors, so you get a data frame with a single factor variable.

1.2.4.3 Mis-specifying the representation of missing values

The file `fem-dot.dat` contains a version of the FEM dataset in which all missing values are represented with a dot. This is a common way of representing missing values, but is not recognized by default by the `read.table()` function, which assumes that missing values are represented by “NA”.

Inspect the file with a text editor, and then see what happens when you read the file in incorrectly:

```
> fem4 <- read.table("data/fem-dot.dat", header=TRUE)
> str(fem4)
```

You should have enough clues by now to work out what went wrong.

You can read the data correctly using the `na.strings` argument

```
> fem4 <- read.table("data/fem-dot.dat", header=TRUE, na.strings=".")
```

1.2.5 Spreadsheet data

Spreadsheets have become a common way of exchanging data. All spreadsheet programs can save a single sheet in *comma-separated variable* (CSV) format, which can then be read into R. There are two functions in R for reading in CSV data: `read.csv()` and `read.csv2()`.

Both of these are wrappers around the `read.table()` function, *i.e.* the `read.table()` function is still doing the work of reading in the data but the `read.csv()` function provides default argument values for reading in CSV file so all you need to do is specify the file name.

You can see what these default arguments are with the `args()` function.

```
> args(read.csv)
> args(read.csv2)
```

See if you can spot the difference between `read.csv` and `read.csv2`.

Explanation: The CSV format is not a single standard. The file format depends on the *locale* of your computer – the settings that determine how numbers are represented. In some countries, the decimal separator is a point “.” and the variable separator in a CSV file is a comma “,”. In other countries, the decimal

separator is a comma “,” and the variable separator is a semi-colon “;”. This is reflected in the different default values for the arguments `sep` and `dec`. The `read.csv()` function is used for the first format and the `read.csv2()` function is used for the second format.

The file `fem.csv` contains the FEM dataset in CSV format. Inspect the file to work out which format is used, and read it into R.

1.2.6 Reading data from the Internet

You can also read in data from a remote web site. The `file` argument of `read.table()` does not need to be a local file on your computer; it can be a Uniform Resource Locator (URL), *i.e.* a web address.

A copy of the file `fem.dat` is held at

<https://www.bendixcarstensen.com/SPE/data/fem.dat>. You can read it in with

```
> fem6 <- read.table("http://www.bendixcarstensen.com/SPE/data/fem.dat",  
+                    header=TRUE)  
> str(fem6)
```

1.2.7 Reading from the clipboard

On Microsoft Windows, you can copy values directly from an open Excel spreadsheet using the clipboard. Highlight the cells you want to copy in the spread sheet and select copy from the pull-down edit menu. Then type `read.table(file="clipboard")` to read the data in.

There are two reasons why this is a bad idea

- It is not reproducible. In order to read the data in again you need to complete exactly the same sequence of mouse moves and clicks, and there is no record of what you did before.
- Copying from the clipboard loses precision. If you have a value 1.23456789 in your spreadsheet, but have formatted the cell so it is displayed to two decimal places, then the value read into R will be the truncated value 1.23.

1.2.8 Binary data

The `foreign` package allows you to read data in binary formats used by other statistical packages. Since R is an open source project, it can only read binary formats that are themselves “open”, in the sense that the standards for reading and writing data are well-documented. For example, there is a function in the `foreign` package for reading SAS XPORT files, a format that has been adopted as a standard by the US Food and Drug Administration (<http://www.sas.com/govedu/fda/faq.html>). However, there is no function in the `foreign` package for reading native SAS binaries (SAS7BDAT files). Other packages are available from CRAN (<http://cran.r-project.org>) that offer the possibility of reading SAS binary files: see the `haven` and `sas7bdat` packages.

The file `fem.dta` contains the FEM dataset in the format used by Stata. Read it into R with

```
> library(foreign)
> fem5 <- read.dta("data/fem.dta")
> head(fem5)
```

The Stata data set contains value and variable labels. Stata variables with value labels are automatically converted to factors.

There is no equivalent of variable labels in an R data frame, but the original variable labels are not lost. They are still attached to the data frame as an invisible *attribute*, which you can see with

```
> attr(fem5, "var.labels")
```

A lot of *meta-data* is attached to the data in the form of attributes. You can see the whole list of attributes with

```
> attributes(fem5)
```

or just the attribute names with

```
> names(attributes(fem5))
```

The `read.dta()` function can only read data from Stata versions 5–12. The R Core Team has not been able to keep up with changes in the Stata format. You may wish to try the `haven` package and the `readstata13` package, both available from CRAN.

1.2.9 Summary

In this exercise we have seen how to create a data frame in R from an external text file. We have also reviewed some common mistakes that result in garbled data.

The capabilities of the `foreign` package for reading binary data have also been demonstrated with a sample Stata data set.

1.3 Tabulation

1.3.1 Introduction

R and its add-on packages provide several different tabulation functions with different capabilities. The appropriate function to use depends on your goal. There are at least three different uses for tables.

The first use is to create simple summary statistics that will be used for further calculations in R. For example, a two-by-two table created by the `table` function can be passed to `fisher.test`, which will calculate odds ratios and confidence intervals. The appearance of these tables may, however, be quite basic, as their principal goal is to create new objects for future calculations.

A quite different use of tabulation is to make “production quality” tables for publication. You may want to generate reports from for publication in paper form, or on the World Wide Web. The package `xtable` provides this capability, but it is not covered by this course.

An intermediate use of tabulation functions is to create human-readable tables for discussion within your work-group, but not for publication. The `Epi` package provides a function `stat.table` for this purpose, and this practical is designed to introduce this function.

1.3.2 The births data

We shall use the births data which concern 500 mothers who had singleton births in a large London hospital. The outcome of interest is the birth weight of the baby, also dichotomised as normal or low birth weight. These data are available in the `Epi` package:

```
> library(Epi)
> data(births)
> names(births)
> head(births)
```

In order to work with this data set we need to transform some of the variables into factors. This is done with the following commands:

```
> births$hyp <- factor(births$hyp, labels=c("normal", "hyper"))
> births$sex <- factor(births$sex, labels=c("M", "F"))
> births$agegrp <- cut(births$matage, breaks=c(20, 25, 30, 35, 40, 45), right=FALSE)
> births$gest4 <- cut(births$gestwks, breaks=c(20, 35, 37, 39, 45), right=FALSE)
```

Now use `str(births)` to examine the modified data frame. We have transformed the binary variables `hyp` and `sex` into factors with informative labels. This will help when displaying the tables. We have also created grouped variables `agegrp` and `gest4` from the continuous variables `matage` and `gestwks` so that they can be tabulated.

1.3.3 One-way tables

The simplest table one-way table is created by

```
> stat.table(index = sex, data = births)
```

This creates a count of individuals, classified by levels of the factor `sex`. Compare this table with the equivalent one produced by the `table` function. Note that `stat.table` has a `data` argument that allows you to use variables in a data frame without specifying the frame.

You can display several summary statistics in the same table by giving a list of expressions to the `contents` argument:

```
> stat.table(index = sex, contents = list(count(), percent(sex)), data=births)
```

Only a limited set of expressions are allowed: see the help page for `stat.table` for details.

You can also calculate marginal tables by specifying `margin=TRUE` in your call to `stat.table`. Do this for the above table. Check that the percentages add up to 100 and the total for `count()` is the same as the number of rows of the data frame `births`. To see how the mean birth weight changes with `sex`, try

```
> stat.table(index = sex, contents = mean(bweight), data=births)
```

Add the count to this table. Add also the margin with `margin=TRUE`. As an alternative to `bweight` we can look at `lowbw` with

```
> stat.table(index = sex, contents = percent(lowbw), data=births)
```

All the percentages are 100! To use the `percent` function the variable `lowbw` must also be in the index, as in

```
> stat.table(index = list(sex,lowbw), contents = percent(lowbw), data=births)
```

The final column is the percentage of babies with low birth weight by different categories of gestation.

1. Obtain a table showing the frequency distribution of `gest4`.
2. Show how the mean birth weight changes with `gest4`.
3. Show how the percentage of low birth weight babies changes with `gest4`.

Another way of obtaining the percentage of low birth weight babies by gestation is to use the `ratio` function:

```
> stat.table(gest4, ratio(lowbw, 1, 100), data=births)
```

This only works because `lowbw` is coded 0/1, with 1 for low birth weight.

Tables of odds can be produced in the same way by using `ratio(lowbw, 1-lowbw)`. The `ratio` function is also very useful for making tables of rates with (say) `ratio(D,Y,1000)` where `D` is the number of failures, and `Y` is the follow-up time. We shall return to rates in a later practical.

1.3.4 Improving the Presentation of Tables

The `stat.table` function provides default column headings based on the `contents` argument, but these are not always very informative. Supply your own column headings using *tagged* lists as the value of the `contents` argument, within a `stat.table` call:

```
> stat.table(gest4, contents = list( N=count(),  
+      "(%)" = percent(gest4)), data=births)
```

This improves the readability of the table. It remains to give an informative title to the index variable. You can do this in the same way: instead of giving `gest4` as the `index` argument to `stat.table`, use a named list:

```
> stat.table(index = list("Gestation time" = gest4), data=births)
```

1.3.5 Two-way Tables

The following call gives a 2×2 table showing the mean birth weight cross-classified by `sex` and `hyp`.

```
> stat.table(list(sex,hyp), contents=mean(bweight), data=births)
```

Add the count to this table and repeat the function call using `margin = TRUE` to calculate the marginal tables. Use `stat.table` with the ratio function to obtain a 2×2 table of percent low birth weight by `sex` and `hyp`. You can have fine-grained control over which margins to calculate by giving a logical vector to the `margin` argument. Use `margin=c(FALSE, TRUE)` to calculate margins over `sex` but not `hyp`. This might not be what you expect, but the `margin` argument indicates which of the index variables are to be **marginalized out**, not which index variables are to remain.

1.3.6 Printing

Just like every other R function, `stat.table` produces an object that can be saved and printed later, or used for further calculation. You can control the appearance of a table with an explicit call to `print()`

There are two arguments to the print method for `stat.table`. The `width` argument which specifies the minimum column width, and the `digits` argument which controls the number of digits printed after the decimal point. This table

```
> odds.tab <- stat.table(gest4, list("odds of low bw" = ratio(lowbw,1-lowbw)),  
+                             data=births)  
> print(odds.tab)
```

shows a table of odds that the baby has low birth weight. Use `width=15` and `digits=3` and see the difference.

1.4 Data manipulation with dplyr

1.4.1 Introduction

In this chapter we will reproduce *more or less* the same outputs as in chapter 1.3 using `tidyverse` packages suit.

The main goal is to familiarize you with some of the main `dplyr` and `tidyverse` features. This is an optional practical for participants that have already good basic R basis. All the rest of the course can be done without knowing `dplyr`.

1.4.2 The births data

A quick description of the `births` data-set (from `Epi` package) can be found in chapter 1.3.2. First of all, load the `Epi` and `dplyr` packages. Then we should (re)load the `births` data-set.

```
> library(Epi)
> suppressPackageStartupMessages(library(tidyverse))
> data(births)
```

1.4.3 tibble vs data.frame

Most `dplyr` functions outputs return `tibble` object instead of `data.frame`. Inspect the class and characteristics of the `births` object.

```
> class(births)
> head(births)
```

Note: This can be summarized using `str` function

```
> str(births)
```

`births` object is a 500 x 8 `data.frame`.

Let's convert `births` to `tibble` format with `as_tibble` function.

```
> births_tbl <- as_tibble(births)
> class(births_tbl)
> births_tbl
> ## another way to visualize data set is to use glimpse function
> glimpse(births_tbl)
```

As you can see `tibble` inherits from `data.frame` which implies that all functions working with `data.frame` objects will work with `tibble` objects. The opposite is not necessary true. `tibble` has a couple of extra features compared to classical `data.frame`. One of them is a slightly more user-friendly console print. The main differences being that `tibble` objects supports grouping/nesting features. Some examples we be done will see latter on.

1.4.4 Piping functions

This is one of the most popular features of **tidyverse** grammar. It enables function chaining in R. Function outputs are passed as input to the following function and so on. It can help to make the code more readable. Here is an example of classic vs piped functions.

```
> head(births, 4)
> births %>% head(4)
```

Note: By default the chained object is given as the first argument to the following function. You can use `.` if this is not the case.

Here is a dummy example where we do not give the first argument to a function but the second one.

```
> 4 %>% head(births, .)
```

1.4.5 mutate columns

mutate will allow you to add and or modify columns in a **data.frame**.

Let's create 2 new variables :

- **agegrp** (5 years mother's age group)
- **gest4** (gestation time split in 4 categories)

And modify 2 others:

- **hyp** (factor version of **hyp**; normal vs hyper)
- **sex** (factor version of **sex**; M vs F)

```
> births_tbl <-
+   births_tbl %>%
+   mutate(
+     ## modify hyp variable (conversion into factor)
+     hyp = factor(hyp, levels = c(0, 1), labels = c("normal", "hyper")),
+     ## creating a new variable agegrp
+     agegrp = cut(matage, breaks = c(20, 25, 30, 35, 40, 45), right = FALSE),
+     ## modify sex variable (conversion into factor)
+     sex = factor(sex, levels = c(1, 2), labels = c("M", "F")),
+     ## creating a new variable gest4 with case_when instead of cut
+     gest4 =
+       case_when(
+         gestwks < 25 ~ 'less than 25 weeks',
+         gestwks >= 25 & gestwks < 30 ~ '25-30 weeks',
+         gestwks >= 30 & gestwks < 35 ~ '30-35 weeks',
+         gestwks >= 35 & gestwks < 40 ~ '35-40 weeks',
+         gestwks >= 40 ~ 'more than 40 weeks'
+       )
+   )
> births_tbl
```

You can see in the table columns header the type of data contained in each column. For instance **<dbl>** stands for double (i.e. numeric value) and **fct** stands for factor. In R **data.frame** (/ **tibble**) data type have to be the same within a column (e.g. numeric only) but can be of different type across columns.

Notes that **case_when** function do not return a **factor** but a **character** variable in this case. You will have to force the conversion to **factor** if needed.

1.4.6 select columns, filter and arrange rows

`select` is used for column sub-setting while `filter` is for row sub-setting. They are equivalent to the `[]` in R base language.

Let's display a table where only babies' `id`, `sex`, `bweight` and mothers' `agegrp` are kept for babies with a `bweight` greater than 4000g.

```
> births_tbl %>%
+   ## select only id, women age group, sex and birth weight of the baby
+   select(id, agegrp, sex, bweight) %>%
+   ## keep only babies weighing more than 4000g
+   filter(bweight > 4000)
```

`select` can also be useful to reorder and rename columns.

`arrange` is a nice feature to reorder observations according to chosen attributes.

Let's rename `agegrp`, `sex` and `bweight` with more explicit labels and reorder the table according to babies' decreasing birth weight.

```
> births_tbl %>%
+   ## select only id, women age group, sex and birth weight of the baby
+   select(
+     id,
+     'Age group' = agegrp,
+     Sex = sex,
+     'Birth weight' = bweight
+   ) %>%
+   ## rearrange rows to put the heaviest newborn on top
+   arrange(desc(`Birth weight`))
```

Note: `tibble` supports blank spaces in the column names which can be handy for final table rendering. When you want to work with columns with blank spaces, do not forget to use the “ (back-quote).

Let's do the same but arranging the table by decreasing birth weights within each sex.

```
> births_tbl %>%
+   ## select only id, women age group, sex and birth weight of the baby
+   select(
+     id,
+     'Age group' = agegrp,
+     Sex = sex,
+     'Birth weight' = bweight
+   ) %>%
+   ## rearrange rows to put the heaviest newborn on top
+   arrange(Sex, desc(`Birth weight`))
```

1.4.7 group_by and summarise data

One of the most valuable features of `dplyr` is the ability to aggregate data sharing a common attribute to process by group operations.

Here we want to compute the number of boys and girls in the data-set.

The idea here is to split the `births` table in 2. One for boys, the other for girls and to count the number of rows of each sub-table.

```
> births.01 <-
+   births_tbl %>%
+   ## group the data according to the sex attribute
+   group_by(sex) %>%
+   ## count the number of rows/individuals in each group
+   summarise(
+     count = n()
+   )
> births.01
```

Note: `n` function is equivalent to `nrow`

Now we have the number of boys and girls, we can compute the percentage of newborns in each sex group.

```
> births.02 <-
+   births.01 %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )
```

Trick: most of `dplyr` functions can be applied with an embedded condition using `across` function. This can be very handy in some cases.

As an illustration if you want to calculate the `sum` of every `birth.02` numerical columns

```
> births.03 <-
+   births_tbl %>%
+   select(gest4, sex, gestwks, bweight, matage) %>%
+   group_by(gest4, sex) %>%
+   summarise(
+     across(
+       where(is.numeric),
+       ~ mean(.x, na.rm = TRUE)
+     ),
+     .groups = 'drop'
+   )
> births.03
```

`across` function supports the purrr-style lambda format, e.g. `mean(.x, na.rm = TRUE)` where `.x` refers to the values from the data set to be passed to the function.

Some other functions ending by `_with` can be used conditionally within `dplyr`. As an example we can rename only columns which are not numeric at once (here we want to make all column names using upper characters) using the combination of `rename_with` and `where`.

```
> births.03 %>%
+   rename_with(toupper, where(~ !is.numeric(.x)))
```

Let's now compute the number of births and the mean birth weight according to newborn gender.

```
> births.05 <-
+   births_tbl %>%
+   group_by(sex) %>%
+   summarise(
+     count = n(),
+     bweight.mean = mean(bweight)
+   )
> births.05
```

With `births.05` table, compute the global mean new birth weight.

Note: with such a table the mean baby's birth weight have to be weighted by number of boys and girls.

```
> births.05 %>%
+   summarise(
+     count.tot = sum(count),
+     bweight.mean.tot = weighted.mean(bweight.mean, count)
+   )
> # this is equivalent to
> births_tbl %>%
+   summarise(
+     count.tot = n(),
+     bweight.mean.tot = mean(bweight)
+   )
```

1.4.8 Multiple grouping

In some cases, we can be interested in looking at more than a single strata. This can be achieved using multiple grouping.

Let's count the number of people per gender and birth weight class (low vs not low)

```
> births.06 <-
+   births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n()
+   )
> births.06
```

Try then to compute the percentage of people in each group.

Look at the difference between the 2 following command lines:

```
> births.06 %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )
> births.06 %>%
+   ungroup() %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )
```

Note: summarizing a data-set will remove the latest level of grouping but not the deeper ones if multiple grouping has been done. In some cases you might have to explicitly ungroup your `data.frame` before doing calculations. In the previous examples, if you do not ungroup the data-set, percentages are computed per gender. Ungrouping will let you compute the overall percentages.

Trick: a good practice is to ungroup all the summarized dataset in order to prevent form confusion. You can do it using the `.group = 'drop'` option in `summarize()`.


```

> ## this tibble will still be grouped by sex
> births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n()
+   )
> ## this tibble will be group free
> births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n(),
+     .groups = 'drop'
+   )
>
>

```

The same exercise can be done using gestation time group (`gest4`) as stratifying variable. Lets compute number and mean birth weights according to gestation time category

```

> births_tbl %>%
+   group_by(gest4) %>%
+   summarise(
+     count = n(),
+     bweight.mean = mean(bweight)
+   )

```

Birth weight increases with gestation time.

We can also spot that in our data-set the gestation time is missing for 10 newborns. We will remove this observation for the rest of the practical session.

Lets cross-tabulate the birth weight category and the gestation time groups.

```

> births_tbl %>%
+   ## keep only the newborn with defined gestational time category
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(lowbw, gest4) %>%
+   ## compute the number of babies in each cross category
+   summarise(
+     count = n()
+   ) %>%
+   ## compute the percentage of babies in each gestational time category per
+   ## birth weight category
+   mutate(
+     percent = count / sum(count, na.rm = TRUE)
+   )

```

Similarly we can be interested in the birth weight distribution per gestational time.

```

> births_tbl %>%
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(gest4, lowbw) %>%
+   summarise(
+     count = n()
+   ) %>%

```

```
+ ## compute the percentage of babies in each birth weight category per gestational
+ ## time category
+ mutate(
+   percent = count / sum(count, na.rm = TRUE)
+ )
```

Note: grouping order matters! and can be confusing so think about ungrouping intermediate tables.

1.4.9 Bind and join tables

Another nice feature of `dplyr` is tables binding and joining functions. To practice we will create 2 fake `tibble`:

- **age** an individual database which contains `pid` (unique individuals id) and `age` in year
- **center** an study center database which contains `pid` (unique individuals id) and `center` (the center where an individual is registered)

```
> age <-
+   tibble(
+     pid = 1:6,
+     age = sample(15:25, size = 6, replace = TRUE)
+   )
> center <-
+   tibble(
+     pid = c(1, 2, 3, 4, 10),
+     center = c('A', 'B', 'A', 'B', 'C')
+   )
> age
> center
```

Now the tables are define we will try to make the linkage between individuals ages and the center they belong to.

First of all let's have a look to `bind_rows` function.

```
> bind_rows(age, center)
```

Is it useful?

Here not really but that can be in other situations (e.g. several individuals data base to merge..).

Note: in `bind_rows`, if columns names do not match, they are fill with `NA`.

Here we want to join the 2 `tibble` according to the common attribute `pid`. Depending on the context you can be interested in joining tables differently. Have a look at the differences between `left_join`, `full_join` and `inner_join`.

```
> ## all individuals from ages are kept
> left_join(age, center, by = c('pid'))
> ## everithing is kept
> full_join(age, center, by = c('pid'))
> ## only the individuals present in both dataset are kept
> inner_join(age, center, by = c('pid'))
```

Can you spot the differences between the commands above?

As an exercise, you can try to compute the individuals' mean age per center.

```
> inner_join(age, center, by = c('pid')) %>%
+   group_by(center) %>%
+   summarise(
+     mean_age = mean(age)
+   )
```

Note: the `by` argument indicates which column should be used to make the join. In some cases, you might have to use several columns to match (e.g. per sex and age group), this can be easily done specifying a vector of column names.

1.4.10 Data Visualization with ggplot2

One of the packages that have contributed to **tidyverse** success is for sure **ggplot2**. We will go more into the details on how to produce graphs with **ggplot2** in another practical. Just a quick example of graphic using **ggplot2**.

Let's create a bar plot to visualize the number of births by women age group.

First you have to create a table with the number of birth per age group.

```
> birth_per_ageg <- births_tbl %>% group_by(agegrp) %>% summarise(total_births = n())

> (gg.01 <-
+   ggplot(birth_per_ageg, aes(x = agegrp, y = total_births)) +
+   geom_bar(stat = "identity"))
```

This graph can be customized adding labels and title to the plot:

```
> (gg.02 <-
+   gg.01 +
+   xlab("Women Age Group") +
+   ylab("Total Births") +
+   ggtitle("Number of Births per Women Age Group"))
```

As you can see, plots from **ggplot** family are built sequentially using the `+` operator for each additional element.

1.4.11 String manipulation with stringr

Another popular **tidyverse** popular package is **stringr** package. This package is specialized in the string manipulation. Here are couple of examples.

Let's create a character vector with the following elements representing country names: "Estonia", "Finland", "Denmark", "United Kingdom".

```
> countries <- c("Estonia", "Finland", "Denmark", "United Kingdom")
```

Extract the first three characters from each country name:

```
> country_initials <- str_sub(countries, start = 1, end = 3)
```

Convert all country names to uppercase:

```
> countries_upper <- str_to_upper(countries)
```

Replace "United" with "Utd" in each country name:

```
> countries_modified <- str_replace(countries, "United", "Utd")
```

Find the positions of the letter "n" in each country name:

```
> a_positions <- str_locate_all(countries, "n")
```

As you can see, the output of `str_locate_all` is a list (one element per character string) containing a 2 column table with one line for each match. The first column (start) being the position of the beginning of the match and the second one (end) being the end of the match. In our case, since we are searching for a single character match, this 2 indexes are always the same.

Count the number of characters in each country name:

```
> character_counts <- str_length(countries)
```

These examples demonstrate various string manipulation operations using the **stringr** package. You can modify the exercises, combine several operations or explore other string manipulation functions provided by **stringr** to further practice and enhance your skills in manipulating and analyzing text data.

1.4.12 purrrr package to apply functions to list

Among my favorite **tidyverse** packages, you will find **purrr**. This package contains several functions that are very similar to **lapply** function.

The simplest example could be to apply the same function to a list of elements. As an example let's add "country: " in front of all our

Apply a function to each element of the vector using `map()`. Here producing the mean of some grades per class:

```
> grades <-  
+   list(  
+     c1 = c(80, 85, 90),  
+     c2 = c(75, 70, 85, 88),  
+     c3 = c(90, 85, 95)  
+   )  
> mean_grades <- map(grades, mean)
```

By default `map()` return a list. One of the nice feature of **purrr** functions is to be able to specify the type of output you want (e.g. `_dbl` for numeric, `_chr` for characters, ...). Check and try to explain the differences between the following command lines:

```
> map(grades, mean)  
> map_dbl(grades, mean)  
> map_chr(grades, mean)  
> map_df(grades, mean)
```

Other nice features of `map` like functions is the availability to support more than one argument. `map2()` for 2 arguments and `pmap()` for more than 2. This can be very handy in some conditions. If you are interested you can have a look to this function help file and play with the examples.

`purrr` package has also a set of functions that can be used to apply iteratively a function using `reduce` and/or `accumulate`. The 2 function behave the same way, it takes the 2 first element of a list, apply a function. The results of the first operation is combine with the third element of the list in the same function and so on.. The only difference is that `accumulate` return intermediate results while `reduce` return only the final results.

Here an example of the cumulative product of the 10 first numbers.

```
> 1:10 %>% reduce(`*`)
> 1:10 %>% accumulate(`*`)
```

1.4.13 Bonus: Rendering tables

Once you have produced a nice data-set we can be interested in rendering it in a nice format that can meet presentation/publication expectations. The `kableExtra` table can be useful to achieve this goal.

```
> # if(!require(kableExtra)) install.packages('kableExtra')
> library(kableExtra)
> births.08 <-
+   births_tbl %>%
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(gest4) %>%
+   summarise(
+     N = n()
+   ) %>%
+   mutate(
+     `(%)` = (N / sum(N)) %>% scales::percent()
+   )
> ## default
> births.08
> ## markdown flavor (useful fo automatic report production with knitr)
> # births.08 %>%
> #   knitr::kable(format = 'markdown')
>
> ## create an html version of the table and save it on the hard drive
> births.08 %>%
+   kable() %>%
+   kable_styling(
+     bootstrap_options = c("striped", "hover", "condensed", "responsive"),
+     full_width = FALSE
+   ) %>%
+   save_kable(file = 'births.08.html', self_contained = TRUE)
```

1.5 Graphics in R

There are three kinds of plotting functions in R:

1. Functions that generate a new plot, e.g. `hist()` and `plot()`.
2. Functions that add extra things to an existing plot, e.g. `lines()` and `text()`.
3. Functions that allow you to interact with the plot, e.g. `locator()` and `identify()`.

The normal procedure for making a graph in R is to make a fairly simple initial plot and then add on points, lines, text etc., preferably in a script.

1.5.1 Simple plot on the screen

Load the births data and get an overview of the variables:

```
> library( Epi )
> data( births )
> str( births )
```

Now look at the birthweight distribution with

```
> hist(births$bweight)
```

The histogram can be refined – take a look at the possible options with

```
> help(hist)
```

and try some of the options, for example:

```
> hist(births$bweight, col="gray", border="white")
```

To look at the relationship between birthweight and gestational weeks, try

```
> with(births, plot(gestwks, bweight))
```

You can change the plot-symbol by the option `pch=`. If you want to see all the plot symbols try:

```
> plot(1:25, pch=1:25)
```

4. Make a plot of the birth weight versus maternal age with

```
> with(births, plot(matage, bweight) )
```

5. Label the axes with

```
> with(births, plot(matage, bweight, xlab="Maternal age", ylab="Birth weight (g)") )
```

1.5.2 Colours

There are many colours recognized by R. You can list them all by `colours()` or, equivalently, `colors()` (R allows you to use British or American spelling). To colour the points of birthweight versus gestational weeks, try

```
> with(births, plot(gestwks, bweight, pch=16, col="green") )
```

This creates a solid mass of colour in the centre of the cluster of points and it is no longer possible to see individual points. You can recover this information by overwriting the points with black circles using the `points()` function.

```
> with(births, points(gestwks, bweight, pch=1) )
```

Note: when the number of data points on a scatter plot is large, you may also want to decrease the point size: to get points that are 50% of the original size, add the parameter `cex=0.5` (or another number <1 for different sizes).

1.5.3 Adding to a plot

The `points()` function just used is one of several functions that add elements to an existing plot. By using these functions, you can create quite complex graphs in small steps.

Suppose we wish to recreate the plot of birthweight *vs* gestational weeks using different colours for male and female babies. To start with an empty plot, try

```
> with(births, plot(gestwks, bweight, type="n"))
```

Then add the points with the `points` function.

```
> with(births, points(gestwks[sex==1], bweight[sex==1], col="blue"))
> with(births, points(gestwks[sex==2], bweight[sex==2], col="red"))
```

To add a legend explaining the colours, try

```
> legend("topleft", pch=1, legend=c("Boys", "Girls"), col=c("blue", "red"))
```

which puts the legend in the top left hand corner.

Finally we can add a title to the plot with

```
> title("Birth weight vs gestational weeks in 500 singleton births")
```

1.5.3.1 Using indexing for plot elements

One of the most powerful features of R is the possibility to index vectors, not only to get subsets of them, but also for repeating their elements in complex sequences.

Putting separate colours on males and female as above would become very clumsy if we had a 5 level factor instead of sex.

Instead of specifying one color for all points, we may specify a vector of colours of the same length as the `gestwks` and `bweight` vectors. This is rather tedious to do directly, but R allows you to specify an expression anywhere, so we can use the fact that `sex` takes the values 1 and 2, as follows:

First create a colour vector with two colours, and take look at `sex`:

```
> c("blue","red")
> births$sex
```

Now see what happens if you index the colour vector by sex:

```
> c("blue","red")[births$sex]
```

For every occurrence of a 1 in `sex` you get "blue", and for every occurrence of 2 you get "red", so the result is a long vector of "blue"s and "red"s corresponding to the males and females. This can now be used in the plot:

```
> with(births, plot( gestwks, bweight, pch=16, col=c("blue","red")[sex]) )
```

The same trick can be used if we want to have a separate symbol for mothers over 40 say. We first generate the indexing variable:

```
> births$oldmum <- ( births$matage >= 40 ) + 1
```

Note we add 1 because (`matage >= 40`) generates a logic variable, so by adding 1 we get a numeric variable with values 1 and 2, suitable for indexing:

```
> with(births, plot( gestwks, bweight, pch=c(16,3)[oldmum], col=c("blue","red")[sex] ))
```

so where `oldmum` is 1 we get `pch=16` (a dot) and where `oldmum` is 2 we get `pch=3` (a cross).

R will accept any kind of complexity in the indexing as long as the result is a valid index, so you don't need to create the variable `oldmum`, you can create it on the fly:

```
> with(births, plot( gestwks, bweight, pch=c(16,3)[(matage>=40)+1], col=c("blue","red")[sex] ))
```

1.5.3.2 Generating colours

R has functions that generate a vector of colours for you. For example,

```
> rainbow(4)
```

produces a vector with 4 colours (not immediately human readable, though). There are a few other functions that generates other sequences of colours, type `?rainbow` to see them. The `color` function (or `colour` function if you prefer) returns a vector of the colour names that R knows about. These names can also be used to specify colours.

Gray-tones are produced by the function `gray` (or `grey`), which takes a numerical argument between 0 and 1; `gray(0)` is black and `gray(1)` is white. Try:

```
> plot( 0:10, pch=16, cex=3, col=gray(0:10/10) )
> points( 0:10, pch=1, cex=3 )
```

1.5.4 Saving your graphs for use in other documents

If you need to use the plot in a report or presentation, you can save it in a graphics file. Once you have generated the script (sequence of R commands) that produce the graph (and it looks ok on screen), you can start a non-interactive graphics device and then re-run the script.

Instead of appearing on the screen, the plot will now be written directly to a file. After the plot has been completed you will need to close the device again in order to be able to access the file. Try:


```
> pdf(file="bweight_gwks.pdf", height=4, width=4)
> with(births, plot( gestwks, bweight, col=c("blue","red")[sex]) )
> legend("topleft", pch=1, legend=c("Boys","Girls"), col=c("blue","red"))
> dev.off()
```

This will give you a portable document file `bweight_gwks.pdf` with a graph which is 4 inches tall and 4 inches wide.

Instead of *pdf*, other formats can be used (*jpg*, *png*, *tiff*, ...). See `help(Devices)` for the available options.

In window-based environments (R GUI for Windows, R-Studio) you may also use the menu (`File` → `Save as` ... or `Export`) to save the active graph as a file and even copy-paste may work (from R graphics window to Word, for instance) – however, writing it manually into the file is recommended for reproducibility purposes (in case you need to redraw your graph with some modifications).

1.5.5 The `par()` command

It is possible to manipulate any element in a graph, by using the graphics options. These are collected on the help page of `par()`. For example, if you want axis labels always to be horizontal, use the command `par(las=1)`. This will be in effect until a new graphics device is opened.

Look at the typewriter-version of the help-page with

```
> help(par)
```

or better, use the the html-version through `Help` → `Html help` → `Packages` → `graphics` → `P` → `par`.

It is a good idea to take a print of this (having set the text size to “smallest” because it is long) and carry it with you at any time to read in buses, cinema queues, during boring lectures etc. Don’t despair, few R-users can understand what all the options are for.

`par()` can also be used to ask about the current plot, for example `par("usr")` will give you the exact extent of the axes in the current plot.

If you want more plots on a single page you can use the command

```
> par( mfrow=c(2,3) )
```

This will give you a layout of 2 rows by 3 columns for the next 6 graphs you produce. The plots will appear by row, i.e. in the top row first. If you want the plots to appear columnwise, use `par(mfcol=c(2,3))` (you still get 2 rows by 3 columns).

To restore the layout to a single plot per page use

```
> par(mfrow=c(1,1))
```

If you want a more detailed control over the layout of multiple graphs on a single page look at `?layout`.

1.5.6 Interacting with a plot

The `locator()` function allows you to interact with the plot using the mouse. Typing `locator(1)` shifts you to the graphics window and waits for one click of the left mouse button. When you click, it will return the corresponding coordinates.

You can use `locator()` inside other graphics functions to position graphical elements exactly where you want them. Recreate the birth-weight plot,

```
> with(births, plot(gestwks, bweight, col = c("blue", "red")[sex]) )
```

and then add the legend where you wish it to appear by typing

```
> legend(locator(1), pch=1, legend=c("Boys", "Girls"), col=c("blue", "red") )
```

The `identify()` function allows you to find out which records in the data correspond to points on the graph. Try

```
> with(births, identify(gestwks, bweight))
```

When you click the left mouse button, a label will appear on the graph identifying the row number of the nearest point in the data frame `births`. If there is no point nearby, R will print a warning message on the console instead. To end the interaction with the graphics window, right click the mouse: the `identify` function returns a vector of identified points.

1. Use `identify()` to find which records correspond to the smallest and largest number of gestational weeks and view the corresponding records:

```
> with(births, births[identify(gestwks, bweight), ])
```

1.6 Simple simulation

Monte Carlo methods are computational procedures dealing with simulation of artificial data from given probability distributions with the purpose of learning about the behaviour of phenomena involving random variability. These methods have a wide range of applications in statistics as well as in several branches of science and technology. By solving the following exercises you will learn to use some basic tools of statistical simulation.

1. Whenever using a *random number generator* (RNG) for a simulation study (or for another purpose, such as for producing a randomization list to be used in a clinical trial or for selecting a random sample from a large cohort), it is a good practice to set first the *seed*. It is a number that determines the initial state of the RNG, from which it starts creating the desired sequence of pseudo-random numbers. Explicit specification of the seed enables the reproducibility of the sequence. – Instead of the number 5462319 below you may use your own seed of choice.

```
> set.seed(5462319)
```

2. Generate a random sample of size 20 from a normal distribution with mean 100 and standard deviation 10. Draw a histogram of the sampled values and compute the conventional summary statistics

```
> x <- rnorm(20, 100, 10)
> hist(x)
> c(mean(x), sd(x))
```

Repeat the above lines and compare the results.

3. Now replace the sample size 20 by 1000 and run again twice the previous command lines with this size but keeping the parameter values as before. Compare the results between the two samples here as well as with those in the previous item.
4. Generate 500 observations from a Bernoulli(p) distribution, or Bin(1, p) distribution, taking values 1 and 0 with probabilities p and $1 - p$, respectively, when $p = 0.4$:

```
> X <- rbinom(500, 1, 0.4)
> table(X)
```

5. Now generate another 0/1 variable Y , being dependent on previously generated X , so that $P(Y = 1|X = 1) = 0.2$ and $P(Y = 1|X = 0) = 0.1$.

```
> Y <- rbinom(500, 1, 0.1*X+0.1)
> table(X, Y)
> prop.table(table(X, Y), 1)
```

6. Generate data obeying a simple linear regression model $y_i = 5 + 0.1x_i + \varepsilon_i$, $i = 1, \dots, 100$, in which $\varepsilon_i \sim N(0, 10^2)$, and x_i values are integers from 1 to 100. Plot the (x_i, y_i) -values, and estimate the parameters of that model.

```
> x <- 1:100
> y <- 5 + 0.1*x + rnorm(100,0,10)
> plot(x,y)
> abline(lm(y~x))
> summary(lm(y~x))$coef
```

Are your estimates consistent with the data-generating model? Run the code a couple of times to see the variability in the parameter estimates.

1.7 Analysis of hazard rates, their ratios and differences

This exercise is *very* prescriptive, so you should make an effort to really understand everything you type into R. Consult the relevant slides of the lecture on “Poisson regression for rates ...”

1.7.1 Hand calculations for a single rate

Let λ be the true **hazard rate** or theoretical incidence rate of a given outcome event. Its estimator is the empirical **incidence rate** $\hat{\lambda} = D/Y = \text{no. cases/person-years}$. Recall that the standard error of the empirical rate is $\text{SE}(\hat{\lambda}) = \hat{\lambda}/\sqrt{D}$.

The simplest approximate 95% confidence interval (CI) for λ is given by

$$\hat{\lambda} \pm 1.96 \times \text{SE}(\hat{\lambda})$$

An alternative approach is based on logarithmic transformation of the empirical rate. The standard error of the empirical log-rate $\hat{\theta} = \log(\hat{\lambda})$ is $\text{SE}(\hat{\theta}) = 1/\sqrt{D}$. Thus, a simple approximate 95% confidence interval for the log-hazard $\theta = \log(\lambda)$ is obtained from

$$\hat{\theta} \pm 1.96/\sqrt{D} = \log(\hat{\lambda}) \pm 1.96/\sqrt{D}$$

When taking the exponential from the above limits, we get another approximate confidence interval for the hazard λ itself:

$$\exp\{\log(\hat{\lambda}) \pm 1.96/\sqrt{D}\} = \hat{\lambda} \times \text{EF},$$

where $\text{EF} = \exp\{1.96 \times \text{SE}[\log(\hat{\lambda})]\}$ is the *error factor* associated with the 95% interval. This approach provides a more accurate approximation with small numbers of cases. (However, both these methods fail when $D = 0$, in which case an *exact* method or one based on *profile-likelihood* is needed.)

1. Suppose 15 outcome events are observed during 5532 person-years in a given study cohort. Let's use R as a simple desk calculator to estimate the underlying hazard rate λ (in 1000 person-years; therefore 5.532) and to get the first version of an approximate confidence interval:

```
> library( Epi )
> options(digits=4) # to cut down decimal points in the output

> D <- 15
> Y <- 5.532 # thousands of years!
> rate <- D / Y
> SE.rate <- rate/sqrt(D)
> c(rate, SE.rate, rate + c(-1.96, 1.96)*SE.rate )
```

2. Compute now the approximate confidence interval using the method based on log-transformation and compare the result with that in the previous item.

```
> SE.logr <- 1/sqrt(D)
> EF <- exp( 1.96 * SE.logr )
> c(log(rate), SE.logr)
> c( rate, EF, rate/EF, rate*EF )
```

1.7.2 Poisson model for a single rate with logarithmic link

You are able to estimate the hazard rate λ and compute its CI with a **Poisson regression model**, as described in the relevant slides in the lecture handout.

Poisson regression is a **generalized linear model** in which the **family**, *i.e.* the distribution of the response variable, is assumed to be the Poisson distribution. The most commonly applied **link function** in Poisson regression is the natural logarithm; log for short.

There are several ways of fitting a Poisson regression with these specifications in R.

3. The traditional way, described many textbooks and applied in most software, is based on using the number of events D as the response and the logarithm of person-years Y as an **offset** term.

– Fit now to the given data a simple Poisson model containing only the intercept term, save the results into a model object `m`, and print a summary of the results.

```
> m <- glm( D ~ 1, family=poisson(link=log), offset=log(Y) )
> summary( m )
```

Compare the figures below “Coefficients” to those you obtained from your hand calculations for `log(rate)` in section 1.6.2, item 2. – What did you get?

4. The summary method produces too much output for our purposes. You can extract CIs for the model parameters directly from the fitted model on the scale determined by the link function with function `ci.lin()`. Thus, the estimate, its SE, and confidence limits for the log-rate $\theta = \log(\lambda)$ are obtained by:

```
> ci.lin( m )
```

However, to get the point estimate and the confidence limits for the hazard rate $\lambda = \exp(\theta)$ itself on the original scale, the results must be exp-transformed:

```
> ci.lin( m, Exp=TRUE)
```

To get just the point estimate and CI for λ from log-transformed quantities you are recommended to use function `ci.exp()`, which is actually a wrapper of `ci.lin()`:

```
> ci.exp( m )
> ci.lin( m, Exp=TRUE)[, 5:7]
```

Both functions are found from `Epi` package. – Note that the test statistic and P -value are rarely interesting quantities for a single rate.

5. There is another method for fitting Poisson regression, which overcomes some of the limitations in the traditional method. A family object `poisreg`, a modified version of the original `poisson` family object, is available in package `Epi`. When using this, the response is defined as a *matrix* of two columns: numbers of cases D and person-years Y , these being combined into a matrix by `cbind(D,Y)`. No specification of **offset** is needed.

```
> mreg <- glm( cbind(D, Y) ~ 1, family=poisreg(link=log) )
> ci.exp( mreg )
```

In this course we endorse the use of family `poisreg` because of its advantages in more general settings.

1.7.3 Poisson model for a single rate with identity link

The approach leaning on having the number of cases D as the response and $\log(Y)$ as an offset, is limited only to models with log link. A major advantage of the `poisreg` family is that it allows a straightforward use of the *identity* link, too. With this link the response variable is the same, but the parameters to be directly estimated are now the rates itself and their differences, not the log-rates and their differences as with the log link.

6. Fit a Poisson model with identity link to our simple data, and use `ci.lin()` to produce the estimate and the confidence interval for the hazard rate from this model:

```
> mid <- glm( cbind(D,Y) ~ 1, family=poisreg(link=identity) )
> ci.lin( mid )
> ci.lin( mid )[, c(1,5,6)]
```

How is the coefficient of this model interpreted? Verify that you actually get the same rate estimate and CI as in section 1.6.1, item 1.

1.7.4 Poisson model assuming the same rate for several periods

Now, suppose the events and person years are collected over three distinct periods.

7. Read in the data and compute period-specific rates

```
> Dx <- c(3,7,5)
> Yx <- c(1.412,2.783,1.337)
> Px <- 1:3
> rates <- Dx/Yx
> rates
```

8. Using these data, fit the same model with log link as in section 1.6.2, assuming a common single hazard λ for the separate periods. Compare the result from the previous ones

```
> m3 <- glm( cbind(Dx,Yx) ~ 1, family=poisreg(link=log) )
> ci.exp( m3 )
```

9. Now test whether the rates are the same in the three periods: Try to fit a model with the period as a factor in the model:

```
> mp <- glm( cbind(Dx,Yx) ~ factor(Px), family=poisreg(link=log) )
> ci.exp(mp)
```

Compare the goodness-of-fit of the two models using `anova()` with the argument `test="Chisq"`:

```
> anova( m3, mp, test="Chisq" )
```

Compare the test statistic to the deviance of the model `mp`. – What is the deviance indicating?

1.7.5 Analysis of rate ratio

We now switch to comparison of two rates λ_1 and λ_0 , i.e. the hazard in an exposed group vs. that in an unexposed one.

Consider first estimation of the **hazard ratio** or the underlying “true” rate ratio $\rho = \lambda_1/\lambda_0$ between the groups. Suppose we have pertinent empirical data (cases and person-times) from both groups, (D_1, Y_1) and (D_0, Y_0) . The point estimate of ρ is the empirical **incidence rate ratio**

$$\hat{\rho} = \text{RR} = \frac{\hat{\lambda}_1}{\hat{\lambda}_0} = \frac{D_1/Y_1}{D_0/Y_0}$$

The variance of $\log(\text{RR})$, that is, the difference of the log of the empirical rates, $\log(\hat{\lambda}_1) - \log(\hat{\lambda}_0)$, is commonly estimated as

$$\begin{aligned} \text{var}(\log(\text{RR})) &= \text{var}\{\log(\hat{\lambda}_1/\hat{\lambda}_0)\} = \text{var}\{\log(\hat{\lambda}_1)\} + \text{var}\{\log(\hat{\lambda}_0)\} \\ &= 1/D_1 + 1/D_0 \end{aligned}$$

Based on a similar argument as before, an approximate 95% CI for the true rate ratio λ_1/λ_0 is then:

$$\text{RR} \times \exp\left(1.96\sqrt{\frac{1}{D_1} + \frac{1}{D_0}}\right)$$

Suppose you have 15 events during 5532 person-years in an unexposed group and 28 events during 4783 person-years in an exposed group:

10. Calculate the incidence rates in the two groups, their ratio, and the CI of the true hazard ratio ρ by direct application of the above formulae:

```
> D0 <- 15 ; D1 <- 28
> Y0 <- 5.532 ; Y1 <- 4.783
> R1 <- D1/Y1; R0 <- D0/Y0
> RR <- R1/R0
> SE.lrr <- sqrt(1/D0+1/D1)
> EF <- exp( 1.96 * SE.lrr)
> c( R1, R0, RR, RR/EF, RR*EF )
```

11. Now achieve this using a Poisson model. For that we first combine the group-specific numbers into pertinent vectors and specify a factor to represent the contrast between the exposed and the unexposed group

```
> D <- c(D0,D1) ; Y <- c(Y0,Y1); expos <- 0:1
> mm <- glm( cbind(D,Y) ~ factor(expos), family=poisreg(link=log) )
```

What do the parameters mean in this model?

12. You can extract the estimation results for exponentiated parameters in two ways, as before:

```
> ci.exp( mm )
> ci.lin( mm, Exp=TRUE ) [,5:7]
```


1.7.6 Analysis of rate difference

For the **hazard difference** $\delta = \lambda_1 - \lambda_0$, the natural estimator is the **incidence rate difference**

$$\hat{\delta} = \hat{\lambda}_1 - \hat{\lambda}_0 = D_1/Y_1 - D_0/Y_0 = \text{RD}.$$

Its variance is just the sum of the variances of the two rates

$$\begin{aligned} \text{var}(\text{RD}) &= \text{var}(\hat{\lambda}_1) + \text{var}(\hat{\lambda}_0) \\ &= D_1/Y_1^2 + D_0/Y_0^2 \end{aligned}$$

13. Use this formula to compute the point estimate of the rate difference λ and a 95% confidence interval for it:

```
> RD <- diff( D/Y )      ## or RD <- R1 - R0
> SED <- sqrt( sum( D/Y^2 ) )
> c( R1, R0, RD, SED, RD+c(-1,1)*1.96*SED )
```

14. Verify that this is the confidence interval you get when you fit an additive model (obtained by identity link) with exposure as a factor:

```
> ma <- glm( cbind(D,Y) ~ factor(expos),
+           family=poisreg(link=identity) )
> ci.lin( ma )[, c(1,5,6)]
```

1.7.7 Optional/Homework: Identity link with weighting

Do this only after you have done the other exercises of this session, i.e. those in section 1.7.

15. There is yet another way of fitting Poisson regression models in R. It is based on using the original family **poisson** but having the empirical rate $\hat{\lambda} = D/Y$ as a **scaled** Poisson response, and the person-years Y as a **weight** variable instead of an offset term. – When applying this procedure, it will give you a warning about a non-integer response in a Poisson model, but you can ignore this warning

```
> mwei <- glm( D/Y ~ 1, family=poisson(link=log), weight=Y )
> ci.exp( mwei )
```

Verify that this gave the same results as above.

16. Repeat the model fitting parts in sections 1.6.5, and 1.6.6. using this approach based on weighting, in which the response is D/Y , the family is **poisson**, and **weight** = Y . Verify that you got similar results.

1.7.8 Optional/Homework: Calculations using matrix tools

NB. *This subsection requires some familiarity with matrix algebra. Do this only after you have done the other exercises of this session.*

17. Explore the function `ci.mat()`, which lets you use matrix multiplication (operator `'%*%'` in R) to produce a confidence interval from an estimate and its standard error (or CIs from whole columns of estimates and SEs):

```
> ci.mat
> ci.mat()
```

As you see, this function returns a 2×3 matrix (2 rows, 3 columns) containing familiar numbers.

18. When you combine the single rate and its standard error into a row vector of length 2, i.e. a 1×2 matrix, and multiply this by the 2×3 matrix above, the computation returns a 1×3 matrix containing the point estimate and the confidence limit. – Apply this method to the single rate calculations in 1.6.1; first creating the 1×2 matrix and then performing the matrix multiplication.

```
> rateandSE <- c( rate, SE.rate )
> rateandSE
> rateandSE %*% ci.mat()
```

19. When the confidence interval is based on the log-rate and its standard error, the result is obtained by appropriate application of the exp-function on the pertinent matrix product

```
> lograndSE <- c( log(rate), SE.logr )
> lograndSE
> exp( lograndSE %*% ci.mat() )
```

20. For computing the rate ratio and its CI as in 1.6.5, matrix multiplication with `ci.mat()` should give the same result as there:

```
> exp( c( log(RR), SE.lrr ) %*% ci.mat() )
```

21. The main argument in function `ci.mat()` is `alpha`, which sets the confidence level: $1 - \alpha$. The default value is `alpha = 0.05`, corresponding to the level $1 - 0.05 = 95\%$. If you wish to get the confidence interval for the rate ratio at the 90 % level ($= 1 - 0.1$), for instance, you may proceed as follows:

```
> ci.mat( alpha=0.1 )
> exp( c( log(RR), SE.lrr ) %*% ci.mat(alpha=0.1) )
```

22. Look again to the model used to analyse the rate ratio in 2.7.5. Often one would like to get simultaneously both the rates and the ratio between them. This can be achieved in one go using the *contrast matrix* argument `ctr.mat` to `ci.lin()` or `ci.exp()`. Try:

```
> CM <- rbind( c(1,0), c(1,1), c(0,1) )
> rownames( CM ) <- c("rate 0","rate 1","RR 1 vs. 0")
> CM
> mm <- glm( D ~ factor(expos),
+           family=poisson(link=log), offset=log(Y) )
> ci.exp( mm, ctr.mat=CM )
```

23. Use the same machinery to the additive model to get the rates and the rate-difference in one go. Note that the annotation of the resulting estimates are via the column-names of the contrast matrix.

```
> rownames( CM ) <- c("rate 0","rate 1","RD 1 vs. 0")
> ma <- glm( cbind(D,Y) ~ factor(expos),
+           family=poisreg(link=identity) )
> ci.lin( ma, ctr.mat=CM )[, c(1,5,6)]
```

1.8 Logistic regression (GLM)

1.8.1 Malignant melanoma in Denmark

In the mid-80s a case-control study on risk factors for malignant melanoma was conducted in Denmark (Østerlind et al. The Danish case-control study of cutaneous malignant melanoma I: Importance of host factors. *Int J Cancer* 1988; 42: 200-206).

The cases were patients with skin melanoma (excluding lentigo melanoma), newly diagnosed from 1 Oct, 1982 to 31 March, 1985, aged 20-79, from East Denmark, and they were identified from the Danish Cancer Registry.

The controls (twice as many as cases) were drawn from the residents of East Denmark in April, 1984, as a random sample stratified by sex and age (within the same 5 year age group) to reflect the sex and age distribution of the cases. This is called group matching, and in such a study, it is necessary to control for age and sex in the statistical analysis. (Yes indeed: In spite of the fact that stratified sampling by sex and age removed the statistical association of these variables with melanoma from the final case-control data set, the analysis must control for variables which determine the probability of selecting subjects from the base population to the study sample.)

The population of East Denmark is a dynamic one. Sampling the controls only at one time point is a rough approximation of *incidence density sampling*, which ideally would spread out over the whole study period. Hence the exposure odds ratios calculable from the data are estimates of the corresponding hazard rate ratios between the exposure groups.

After exclusions, refusals etc., 474 cases (92% of eligible cases) and 926 controls (82%) were interviewed. This was done face-to-face with a structured questionnaire by trained interviewers, who were not informed about the subject's case-control status.

For this exercise we have selected a few host variables from the study in an ascii-file, `melanoma.dat`. The variables are listed in table 2.1.

Table 1.1: *Variables in the melanoma dataset.*

Variable	Units or Coding	Type	Name
Case-control status	1=case, 0=control	numeric	<code>cc</code>
Sex	1=male, 2=female	numeric	<code>sex</code>
Age at interview	age in years	numeric	<code>age</code>
Skin complexion	0=dark, 1=medium, 2=light	numeric	<code>skin</code>
Hair colour	0=dark brown/black, 1=light brown, 2=blonde, 3=red	numeric	<code>hair</code>
eye colour	0=brown, 1=grey, green, 2=blue	numeric	<code>eyes</code>
Freckles	1=many, 2=some, 3=none	numeric	<code>freckles</code>
Naevi, small	no. naevi < 5mm	numeric	<code>nvsmall</code>
Naevi, largs	no. naevi ≥ 5mm	numeric	<code>nvlarge</code>

1.8.2 Reading the data

Start R and load the `Epi` package using the function `library()`. Read the data set from the file `melanoma.dat` found in the course website to a data frame with name `mel` using the `read.table()` function. Remember to specify that missing values are coded ".", and that variable names are in the first line of the file. View the overall structure of the data frame, and list the first 20 rows of `mel`.

```
> library(Epi)
> mel <- read.table("http://bendixcarstensen.com/SPE/data/melanoma.dat", header=TRUE, na.strings=".", as.is=TRUE)
> str(mel)
> head(mel, n=20)
```

1.8.3 House keeping

The structure of the data frame `mel` tells us that all the variables are numeric (integer), so first you need to do a bit of house keeping. For example the variables `sex`, `skin`, `hair`, `eye` need to be converted to factors, with labels, and `freckles` which is coded 4 for none down to 1 for many (not very intuitive) needs to be recoded, and relabelled.

To avoid too much typing and to leave plenty of time to think about the analysis, these house keeping commands are in a script file called `melanoma-house.r`. You should study this script carefully before running it. The coding of `freckles` can be reversed by subtracting the current codes from 4. Once recoded the variable needs to be converted to a factor with labels "none", etc. Age is currently a numeric variable recording age to the nearest year, and it will be convenient to group these values into (say) 10 year age groups, using `cut`. In this case we choose to create a new variable, rather than change the original.

```
> source("http://bendixcarstensen.com/SPE/data/melanoma-house.r")
```

Look again at the structure of the data frame `mel` and note the changes. Use the command `summary(mel)` to look at the univariate distributions.

This is enough housekeeping for now - let's turn to something a bit more interesting.

1.8.4 One variable at a time

As a first step it is a good idea to start by looking at the numbers of cases and controls by each variable separately, ignoring age and sex. Try

```
> with(mel, table(cc,skin))
> stat.table(skin, contents=ratio(cc,1-cc), data=mel)
```

to see the numbers of cases and controls, as well as the odds of being a case by skin colour

Now use `effx()` to get crude estimates of the hazard ratios for the effect of skin colour.

```
> effx(cc, type="binary", exposure=skin, data=mel)
```

- Look at the crude effect estimates of `hair`, `eyes` and `freckles` in the same way.

1.8.5 Generalized linear models with binomial family and logit link

The function `effx()` is just a wrapper for the `glm()` function, and you can show this by fitting the `glm` directly with

```
> mf <- glm(cc ~ freckles, family="binomial", data=mel)
> round(ci.exp( mf ),2)
>
```

Comparison with the output from `effx()` shows the results to be the same.

Note that in `effx()` the type of response is “binary” whereas in `glm()` the family of probability distributions used to fit the model is “binomial”. There is a 1-1 relationship between type of response and family:

metric	gaussian
binary	binomial
failure/count	poisson

1.8.6 Controlling for age and sex

Because the probability that a control is selected into the study depends on age and sex it is necessary to control for age and sex. For example, the effect of freckles controlled for age and sex is obtained with

```
> effx(cc, typ="binary", exposure=freckles, control=list(age.cat,sex),data=mel)
```

or

```
> mfas <- glm(cc ~ freckles + age.cat + sex, family="binomial", data=mel)
> round(ci.exp(mfas), 2)
```

Do the adjusted estimates differ from the crude ones that you computed with `effx()`?

1.8.7 Likelihood ratio tests

There are 2 effects estimated for the 3 levels of `freckles`, and `glm()` provides a test for each effect separately, but to test for no effect at all of `freckles` you need a likelihood ratio test. This involves fitting two models, one without `freckles` and one with, and recording the change in deviance. Because there are some missing values for freckles it is necessary to restrict the first model to those subjects who have values for freckles.

```
> mas <- glm(cc ~ age.cat + sex, family="binomial", data=subset(mel, !is.na(freckles)) )
> anova(mas, mfas, test="Chisq")
```

The change in residual deviance is $1785.9 - 1737.1 = 48.8$ on $1389 - 1387 = 2$ degrees of freedom. The P -value corresponding to this change is obtained from the upper tail of the cumulative distribution of the χ^2 -distribution with 2 df:

```
> 1 - pchisq(48.786, 2)
```

- There are 3 effects for the 4 levels of hair colour (`hair`). To obtain adjusted estimates for the effect of hair colour and to test the pertinent null hypothesis fit the relevant models, print the and use `anova` to test for no effects of hair colour. Compare the estimates with the crude ones and assess the evidence against the null hypothesis.

1.8.8 Relevelling

From the above you can see that subjects at each of the 3 levels light-brown, blonde, and red, are at greater risk than subjects with dark hair, with similar odds ratios. This suggests creating a new variable `hair2` which has just two levels, dark and the other three. The `Relevel()` function in `Epi` has been used for this in the house keeping script.

- Use `effx()` to compute the odds-ratio of melanoma between persons with red, blonde or light brown hair versus those with dark hair. Reproduce these results by fitting an appropriate glm. Use also a likelihood ratio test to test for the effect of `hair2`.

1.8.9 Controlling for other variables

When you control the effect of an exposure for some variable you are asking a question about what would the effect be if the variable is kept constant. For example, consider the effect of `freckles` controlled for `hair2`. We first stratify by `hair2` with

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex), strata=hair2, data=mel)
```

The effect of freckles is still apparent in each of the two strata for hair colour. Use `effx()` to control for `hair2`, too, in addition to `age.cat` and `sex`.

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex, hair2), data=mel)
```

It is tempting to control for variables without thinking about the question you are thereby asking. This can lead to nonsense.

1.8.10 Stratification using `glm()`

We shall reproduce the output from

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex), strata=hair2, data=mel)
```

using `glm()`. To do this requires a nested model formula:

```
> mfas.h <- glm(cc ~ hair2/freckles + age.cat + sex, family="binomial", data=mel)
> ci.exp(mfas.h)
```

In amongst all the other effects you can see the two effects of freckles for dark hair (1.61 and 2.84) and the two effects of freckles for other hair (1.42 and 3.15).

1.8.11 Naevi

The distributions of `nvsmall` and `nvlarge` are very skew to the right. You can see this with

```
> with(mel, stem(nvsmall))
> with(mel, stem(nvlarge))
```

Because of this it is wise to categorize them into a few classes

- small naevi into four: 0, 1, 2-4, and 5+;

- large naevi into three: 0, 1, and 2+.

This has been done in the house keeping script.

- Look at the joint frequency distribution of these new variables using `with(mel, table())`. Are they strongly associated?
- Compute the sex- and age-adjusted OR estimates (with 95% CIs) associated with the number of small naevi first by using `effx()`, and then by fitting separate glms including `sex`, `age.cat` and `nvsm4` in the model formula.
- Do the same with large naevi `nvlar3`.
- Now fit a glm containing `age.cat`, `sex`, `nvsm4` and `nvlar3`. What is the interpretation of the coefficients for `nvsm4` and `nvlar3`?

1.8.12 Treating freckles as a numeric exposure

The evidence for the effect of `freckles` is already convincing. However, to demonstrate how it is done, we shall perform a linear trend test by treating freckles as a numeric exposure.

```
> mel$fscore<-as.numeric(mel$freckles)
> effx(cc, type="binary", exposure=fscore, control=list(age.cat,sex), data=mel)
```

You can check for linearity of the log odds of being a case with `fscore` by comparing the model containing `freckles` as a factor with the model containing `freckles` as numeric.

```
> m1 <- glm(cc ~ freckles + age.cat + sex, family="binomial", data=mel)
> m2 <- glm(cc ~ fscore + age.cat + sex, family="binomial", data=mel)
> anova(m2, m1, test="Chisq")
```

There is no evidence against linearity ($p = 0.22$).

It is sometimes helpful to look at the linearity in more detail with

```
> m1 <- glm(cc ~ C(freckles, contr.cum) + age.cat + sex, family="binomial",data=mel)
> round(ci.exp(m1 ), 2)
> m2 <- glm(cc ~ fscore + age.cat + sex, family="binomial",data=mel)
> round(ci.exp(m2), 2)
```

The use of `C(freckles, contr.cum)` makes each odds ratio to compare the odds at that level versus the previous level; not against the baseline (except for the 2nd level). If the log-odds are linear then these odds ratios should be the same (and the same as the odds ratio for `fscore` in `m2`).

1.8.13 Graphical displays

The odds ratios (with CIs) can be graphically displayed using function `plotEst()` in `Epi`. It uses the value of `ci.lin()` evaluated on the fitted model object. As the intercept and the effects of age and sex are of no interest, we shall drop the corresponding rows (the 7 first ones) from the matrix produced by `ci.lin()`, and the plot is based just on the 1st, 5th and the 6th column of this matrix:

```
> m <- glm(cc ~ nvsm4 + nvlar3 + age.cat + sex, family="binomial",data=mel)
> plotEst( exp( ci.lin(m)[ 2:5, -(2:4)] ), xlog=T, vref=1 )
```

The `xlog` argument makes the OR axis logarithmic.

1.9 Estimation of effects: simple and more complex

This exercise deals with analysis of metric and binary response variables. We start with simple estimation of effects of a binary, categorical or a numeric explanatory variable, the explanatory or exposure variable of interest. Then evaluation of potential modification and/or confounding by other variables is considered by stratification by and adjustment/control for these variables. Use of function `effx()` for such tasks is introduced together with functions `lm()` and `glm()` that can be used for more general linear and generalized linear models. Finally, more complex spline modelling for the effect of a numeric exposure variable is illustrated.

1.9.1 Response and explanatory variables

Identifying the *response* or *outcome variable* correctly is the key to analysis. The main types are:

- Metric or continuous (a measurement with units).
- Binary (“yes” vs. “no”, coded 1/0), or proportion.
- Failure in person-time, or incidence rate.

All these response variable are numeric.

Variables on which the response may depend are called *explanatory variables* or *regressors*. They can be categorical factors or numeric variables. A further important aspect of explanatory variables is the role they will play in the analysis.

- Primary role: exposure.
- Secondary role: confounder and/or effect-measure modifier.

The word “*effect*” is used here as a general term referring to ways of contrasting or comparing the expected values of the response variable at different levels of an explanatory variable. The main comparative measures or effect measures are:

- Differences in means for a metric response.
- Ratios of odds for a binary response.
- Ratios of rates for a failure or count response.

Other kinds of *contrasts* between exposure groups include (a) ratios of geometric means for positive-valued metric outcomes, (b) differences and ratios between proportions (risk difference and risk ratio), and (c) differences between incidence or mortality rates.

Note that in spite of using the causally loaded word “effect”, we treat *outcome regression* modelling here primarily with descriptive or predictive aims in mind. Traditionally, these types of models have also been used to estimate *causal effects* of exposure variables from the pertinent regression coefficients. More serious causal analysis is introduced in the lecture and practical on Saturday afternoon, and modern approaches to estimate causal effects will be considered on Tuesday afternoon.

1.9.2 Data set births

We shall use the `births` data to illustrate different aspects in estimating effects of various exposures on a metric response variable `bweight` = birth weight, recorded in grams.

1. Load the packages needed in this exercise and the data set, and look at its content

```
> library(Epi)
> library(mgcv)
> data(births)
> str(births)
```

2. Because all variables are numeric we need first to do a little housekeeping. Two of them are directly converted into factors. Categorical versions of two continuous variables are created by function `cut()`.

```
> births$hyp <- factor(births$hyp, labels = c("Normo", "Hyper"))
> births$sex <- factor(births$sex, labels = c("M", "F"))
> births$agegrp <- cut(births$matage,
+   breaks = c(20, 25, 30, 35, 40, 45), right = FALSE)
> births$gest4 <- cut(births$gestwks,
+   breaks = c(20, 35, 37, 39, 45), right = FALSE)
```

3. Have a look at univariate summaries of the different variables in the data; especially the location and dispersion of the distribution of `bweight`.

```
> summary(births)
> with(births, sd(bweight) )
```

1.9.3 Simple estimation with `effx()`, `lm()` and `glm()`

We are ready to analyze the effect of `sex` on `bweight`. A binary explanatory variable, like `sex`, leads to an elementary two-group comparison of group means for a metric response.

1. Comparison of two groups is commonly done by the conventional *t*-test and the associated confidence interval.

```
> with( births, t.test(bweight ~ sex, var.equal=TRUE) )
```

The *P*-value refers to the test of the null hypothesis that there is no effect of `sex` on birth weight (quite an uninteresting null hypothesis in itself!). However, `t.test()` does not provide the point estimate for the effect of sex; only the test result and a confidence interval.

2. The function `effx()` in `Epi` is intended to introduce the estimation of effects in epidemiology, together with the related ideas of stratification and controlling, i.e. adjustment for confounding, without the need for familiarity with statistical modelling. It is in fact a wrapper of function `glm()` that fits generalized linear models.
 - Now, let's do the same analysis with `effx()`

```
> effx(response=bweight, type="metric", exposure=sex, data=births)
```

The estimated effect of sex on birth weight, measured as a difference in means between girls and boys, is -197 g. Either the output from `t.test()` above or the command

```
> stat.table(sex, mean(bweight), data=births)
```

confirms this ($3032.8 - 3229.9 = -197.1$).

3. The same task can easily be performed by `lm()` or by `glm()`. The main argument in both is the *model formula*, the left hand side being the response variable and the right hand side after “ \sim ” defines the explanatory variables and their joint effects on the response. Here the only explanatory variable is the binary factor `sex`. With `glm()` one specifies the `family`, i.e. the assumed distribution of the response variable, but in case you use `lm()`, this argument is not needed, because `lm()` fits only models for metric responses assuming Gaussian distribution.

```
> m1 <- glm(bweight ~ sex, family=gaussian, data=births)
> summary(m1)
```

Note the amount of output that `summary()` method produces. The point estimate plus confidence limits can, though, be concisely obtained by function `ci.lin()` found in `Epi` package.

```
> round( ci.lin(m1)[ , c(1,5,6)] , 1)
```

4. Now, use `effx()` to find the effect of `hyp` (maternal hypertension) on `bweight`.

1.9.4 Factors on more than two levels

The variable `gest4` became as the result of cutting `gestwks` into 4 groups with left-closed and right-open boundaries [20,35) [35,37) [37,39) [39,45).

1. We shall find the effects of `gest4` on the metric response `bweight`.

```
> effx(response=bweight,typ="metric",exposure=gest4,data=births)
```

There are now 3 effect estimates:

```
[35,37) vs [20,35) 857
[37,39) vs [20,35) 1360
[39,45) vs [20,35) 1668
```

The command

```
> stat.table(gest4,mean(bweight),data=births)
```

confirms that the effect of `agegrp` (level 2 vs level 1) is $2590 - 1733 = 857$, etc.

2. Compute these estimates by `lm()` and find out how the coefficients are related to the group means

```
> m2 <- lm(bweight ~ gest4, data = births)
> round( ci.lin(m2)[ , c(1,5,6)] , 1)
```

1.9.5 Stratified effects, and interaction or effect-measure modification

We shall now examine whether and to what extent the “effect” of `hyp` on `bweight`, i.e. the mean difference between hypertensive and normotensive mothers, varies by `gest4` without assigning causal interpretation to the estimated contrasts.

1. The following “interaction plot” shows how the mean `bweight` depends jointly on `hyp` and `gest4`

```
> par(mfrow=c(1,1))
> with( births, interaction.plot(gest4, hyp, bweight) )
```

It appears that the mean difference in `bweight` between hypertensive and normotensive mothers is related to gestational age.

2. Let us get numerical values for the mean differences in the different `gest4` categories:

```
> effx(bweight, type="metric", exposure=hyp, strata=gest4, data=births)
```

The estimated effects of `hyp` in the different strata defined by `gest4` thus range from about -100 g among those with ≥ 39 weeks of gestation to about -700 g among those with < 35 weeks of gestation. The error margin especially around the latter estimate is quite wide, though. The P -value 0.055 from the test for *effect(-measure) modification* indicates weak evidence against the null hypothesis of “no interaction between `hyp` and `gest4`”. On the other hand, this test may well be not very sensitive given the small number of preterm babies in these data.

3. Stratified estimation of effects can also be done by `lm()`, and you should get the same results:

```
> m3 <- lm(bweight ~ gest4/hyp, data = births)
> round( ci.lin(m3)[ , c(1,5,6)], 1)
```

4. An equivalent model with an explicit *product term* or *interaction term* between `gest4` and `hyp` is fitted as follows

```
> m3I <- lm(bweight ~ gest4 + hyp + gest4:hyp, data = births)
> round( ci.lin(m3I)[ , c(1,5,6)], 1)
```

From this output you would find a familiar estimate -673 g for those < 35 gestational weeks. The remaining coefficients are estimates of the interaction effects such that e.g. $515 = -158 - (-673)$ g describes the contrast in the effect of `hyp` on `bweight` between those 35 to < 37 weeks and those < 35 weeks of gestation.

5. Perhaps a more appropriate reference level for the categorized gestational age would be the highest one. Changing the reference level, here to be the 4th category, can be done by `Relevel()` function in the `Epi` package, after which an equivalent interaction model is fitted, now using a shorter expression for it in the model formula:

```
> births$gest4b <- Relevel( births$gest4, ref = 4)
> m3Ib <- lm(bweight ~ gest4b*hyp, data = births)
> round( ci.lin(m3Ib)[ , c(1,5,6)], 1)
```

Notice now the coefficient -91.6 for `hyp`. It estimates the contrast "Hyper" vs. "Normo" on `bweight` among those with ≥ 39 weeks of gestation. The estimate $-88.5 \text{ g} = -180.1 - (-91.6) \text{ g}$ describes the additional effect of `hyp` in the category 37 to 38 weeks of gestation upon that in the reference class.

6. At this stage it is interesting to compare the results from the interaction models to those from the corresponding “main effects” model, in which the effect of `hyp` is assumed not to be modified by `gest4`:

```
> m3M <- lm(bweight ~ gest4 + hyp, data = births)
> round( ci.lin(m3M)[ , c(1,5,6)], 1)
```

The estimate -201 g describing the overall contrast between hypertensive and normotensive mothers is obtained as a weighted average of the stratum-specific estimates that were got by `effx()` above. This assumption or the “no interaction” null hypothesis can formally be tested by a common deviance test.

```
> anova(m3I, m3M)
```

The P -value is practically the same as before, when the interaction was tested in `effx()`. However, in spite of obtaining a “non-significant” result from this test, the possibility of a real effect-measure modification should not be ignored in this case.

7. Now, use `effx()` to stratify (i) the effect of `hyp` on `bweight` by `sex` and then (ii) perform the stratified analysis using the two ways of fitting an interaction model with `lm`.

Look at the results. Is there evidence for the effect of `hyp` being modified by `sex`?

1.9.6 Controlling or adjusting for the effect of `hyp` for `sex`

The effect of `hyp` is *controlled for* – or *adjusted for* – `sex` by first looking at the estimated effects of `hyp` in the two strata defined by `sex`, and then combining these effects if they seem sufficiently similar. In this case the estimated effects were -496 and -380 which look quite similar (and the P -value against “no interaction” was quite large, too), so we can perhaps combine them, and control for `sex`.

1. The combining is done by declaring `sex` as a control variable:

```
> effx(bweight, type="metric", exposure=hyp, control=sex, data=births)
```

2. The same is done with `lm()` as follows:

```
> m4 <- lm(bweight ~ sex + hyp, data = births)
> ci.lin(m4)[ , c(1,5,6)]
```

The estimated effect of `hyp` on `bweight` controlled for `sex` is thus -448 g . There can be more than one control variable, e.g. `control=list(sex, agegrp)`.

Many people go straight ahead and control for variables which are likely to confound the effect of exposure without bothering to stratify first, but usually it is useful to stratify first.

1.9.7 Numeric exposures

If we wished to study the effect of gestation time on the baby's birth weight then `gestwks` is a numeric exposure variable.

1. Assuming that the relationship of the response with `gestwks` is roughly linear (for a continuous response), we can estimate the linear effect of `gestwks`, both with `effx()` and with `lm()` as follows:

```
> effx(response=bweight, type="metric", exposure=gestwks, data=births)
> m5 <- lm(bweight ~ gestwks, data=births) ; ci.lin(m5)[ , c(1,5,6)]
```

We have fitted a simple linear regression model and obtained estimates of the two regression coefficient: `intercept` and `slope`. The linear effect of `gestwks` is thus estimated by the slope coefficient, which is 197 g per each additional week of gestation.

2. You cannot stratify by a numeric variable, but you can study the effects of a numeric exposure stratified by (say) `agegrp` with

```
> effx(bweight, type="metric", exposure=gestwks, strata=agegrp, data=births)
```

You can control/adjust for a numeric variable by putting it in the control list.

1.9.8 Checking the assumptions of the linear model

At this stage it will be best to make some visual check concerning our model assumptions using `plot()`. In particular, when the main argument for the *generic function* `plot()` is a fitted `lm` object, it will provide you some common diagnostic graphs.

1. To check whether `bweight` goes up linearly with `gestwks` try

```
> with(births, plot(gestwks, bweight))
> abline(m5)
```

2. Moreover, take a look at the basic diagnostic plots for the fitted model.

```
> par(mfrow=c(2,2))
> plot(m5)
```

What can you say about the agreement with data of the assumptions of the simple linear regression model, like linearity of the systematic dependence, homoskedasticity and normality of the error terms?

1.9.9 Penalized spline model

We shall now continue the analysis such that the apparently curved effect of `gestwks` is modelled by a *penalized spline*, based on the recommendations of Martyn in his lecture of this morning.

You cannot fit a penalized spline model with `lm()` or `glm()`, Instead, function `gam()` in package `mgcv` can be used for this purpose. Make sure that you have loaded this package.

1. When calling `gam()`, the model formula contains expression '`s(X)`' for any explanatory variable `X`, for which you wish to fit a smooth function

```
> mPs <- gam( bweight ~ s(gestwks), data = births)
> summary(mPs)
```

From the output given by `summary()` you find that the estimated intercept is equal to the overall mean birth weight in the data. The estimated residual variance is given by “**Scale est.**” or from subobject `sig2` of the fitted `gam` object. Taking square root you will obtain the estimated residual standard deviation: 445.2 g.

```
> mPs$sig2
> sqrt(mPs$sig2)
```

The degrees of freedom in this model are not computed as simply as in previous models, and they typically are not integer-valued. However, the fitted spline seems to consume only a little more degrees of freedom as an 3rd degree polynomial model would take.

2. A graphical presentation of the fitted curve together with the confidence and prediction intervals is more informative. Let us first write a short function script to facilitate the task. We utilize function `matshade()` in `Epi`, which creates shaded areas, and function `matlines()` which draws lines joining the pertinent end points over the x -values for which the predictions are computed.

```
> plotFitPredInt <- function( xval, fit, pred, ...)
+ {
+   matshade( xval, fit, lwd=2, alpha=0.2)
+   matshade( xval, pred, lwd=2, alpha=0.2)
+   matlines( xval, fit, lty=1, lwd=c(3,2,2), col=c("red","blue","blue") )
+   matlines( xval, pred, lty=1, lwd=c(3,2,2), col=c("red","green","green") )
+ }
```

3. Finally, create a vector of x -values and compute the fitted/predicted values as well as the interval limits at these points from the fitted model object utilizing function `predict()`. This function creates a matrix of three columns: (1) fitted/predicted values, (2) lower limits, (3) upper limits and make the graph:

```
> nd <- data.frame(gestwks = seq(24, 45, by = 0.25) )
> pr.Ps <- predict( mPs, newdata=nd, se.fit=TRUE )
> str(pr.Ps) # with se.fit=TRUE, only two columns: fitted value and its SE
> fit.Ps <- cbind(pr.Ps$fit,
+               pr.Ps$fit - 2*pr.Ps$se.fit,
+               pr.Ps$fit + 2*pr.Ps$se.fit)
> pred.Ps <- cbind(pr.Ps$fit, # must add residual variance to se.fit^2
+               pr.Ps$fit - 2*sqrt( pr.Ps$se.fit^2 + mPs$sig2),
+               pr.Ps$fit + 2*sqrt( pr.Ps$se.fit^2 + mPs$sig2))
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim=c(24, 45),
+               cex.axis=1.5, cex.lab=1.5) )
> plotFitPredInt(nd$gestwks, fit.Ps, pred.Ps)
```

Compare this with the graph on slide 20 of the lecture we had. Are you happy with the end result?

1.9.10 Analysis of binary outcomes

Instead of investigating the distribution and determinants of birth weight as such, it is common in perinatal epidemiology to consider occurrence of low birth weight; whether birth weight is < 2.5 kg or not. Variable `lowbw` with values 1 and 0 in the `births` data represents that dichotomy. Let's perform some analyses on that outcome to illustrate effect estimation and modelling binary outcome.

1. We start with simple tabulation of the prevalence of `lowbw` by maternal hypertension

```
> stat.table( index=list(hyp, lowbw),
+             contents=list(count(), percent(lowbw)),
+             margins=TRUE, data=births)
```

It seems that the prevalence for hypertensive mothers is about 18 percent points higher, or about three times as high as that for normotensive mothers,

2. The three comparative measures of prevalences can be obtained by `glm()`, whereas `effx()` gives only odds ratio:

```
> binRD <- glm(lowbw ~ hyp, family=binomial(link="identity"), data=births)
> round(ci.lin(binRD)[, c(1,2,5:6)], 3)
> binRR <- glm(lowbw ~ hyp, family=binomial(link="log"), data=births)
> round(ci.lin(binRR, Exp=TRUE)[, c(1,2,5:7)], 3)
> binOR <- glm(lowbw ~ hyp, family=binomial(link="logit"), data=births)
> round(ci.lin(binOR, Exp=TRUE)[, c(1,2,5:7)], 3)
> effx(response=lowbw, type="binary", exposure=hyp, data=births)
```

Check that these results were quite compatible with the “about” estimates given in the previous item. How well is the odds ratio approximating the risk ratio here?

3. The prevalence of low birth weight is expected to be inversely related to gestational age (weeks), as is evident from simple tabulation

```
> stat.table( index=list(gest4, lowbw),
+             contents=list(count(), percent(lowbw)),
+             margins=TRUE, data=births)
```

4. Let's jump right away to spline modelling of this relationship

```
> binm1 <- gam(lowbw ~ s(gestwks), family=binomial(link="logit"), data=births)
> summary(binm1)
> plot(binm1)
```

Inspect the output. Would you agree, that the logit of the prevalence of outcome is almost linearly dependent on `gestwks`?

5. Encouraged by the result of the previous item, we continue the analysis with `glm()` and assuming logit-linearity

```
> binm2 <- glm(lowbw ~ I(gestwks-40), family=binomial(link="logit"), data=births)
> round(ci.lin(binm2, Exp=TRUE)[, c(1,2,5:7)], 3)
```


Inspect the results. How do you interpret the estimated coefficients and their exponentiated values?

6. Instead of fitted logits, it can be more informative to plot the fitted prevalences against `gestwks`, in which we utilize the previously created data frame `nd`

```
> predm2 <- predict(binm2, newdata=nd, type="response")
> plot( nd$gestwks, predm2, type="l")
```

The curve seems to cover practically the whole range of the outcome probability scale with a relatively steep slope between about 33 to 37 weeks.

7. As with numeric birth weight, it may be of interest, whether the effect of `gestwks` is modified by maternal hypertension, so let's fit an interaction model and view the results

```
> binm3 <- glm(lowbw ~ hyp*I(gestwks-40), family=binomial, data=births)
> round(ci.lin(binm3, Exp=TRUE)[, c(1,2,5:7)], 3)
```

How would you interpret the coefficients and their antilogarithms here?

8. Even though there seems to be no sufficient evidence for effect-measure modification, it can be of interest to compare both the fitted lines on the logit scale and the fitted curves on the probability scale between the two groups. Function `qlogis()` returns the value of the logit transformation of the given argument.

```
> predm3hyp <- predict(binm3,
+   newdata=data.frame(hyp="Hyper", nd), type="response")
> predm3nor <- predict(binm3,
+   newdata=data.frame(hyp="Normo", nd), type="response")
> par(mfrow=c(1,2))
> plot( nd$gestwks, qlogis(predm3hyp), type="l")
> lines( nd$gestwks, qlogis(predm3nor), lty=2)
> plot( nd$gestwks, predm3hyp, type="l")
> lines( nd$gestwks, predm3nor, lty=2)
```

The logit-line starts from a higher level and its slope is steeper for the hypertensive mothers, which sounds reasonable. However, the two lines appear to cross at about 38 weeks. On the other hand, the vertical difference of the two probability curves appears discernible only in the area from about 32 to 38 weeks of gestation

When interpreting these findings, one needs to keep in mind that the precision of these curves is very low, because of the small number of outcome cases overall.

1.10 Estimation and reporting of curved effects

This exercise deals with modelling of curved effects of continuous explanatory variables both on a metric response assuming the Gaussian distribution and on a count or rate outcome based on the Poisson family.

In the first part we continue our analysis on gestational age on birth weight focussing on fitting spline models, both unpenalized and a penalized one.

In the second part we analyse the `testisDK` data found in the `Epi` package. It contains the numbers of cases of testis cancer and mid-year populations (person-years) in 1-year age groups in Denmark during 1943–96. In this analysis we apply Poisson regression on the incidence rates treating age and calendar time, first as categorical but then fitting a penalized spline model.

1.10.1 Data births: Simple linear regression and 3rd degree polynomial

Recall what was done in items 17 to 24 of the Exercise on simple estimation of effects, in which a simple linear regression and a 3rd degree polynomial were fitted. The main results are also shown on slides 6, 8, 9, and 20 of the lecture on linear models.

1. Make a basic scatter plot and draw the fitted line from a simple linear regression on it.

```
> library(Epi)
> data(births)
> par(mfrow=c(1,1))
> with(births, plot(gestwks, bweight))
> mlin <- lm( bweight ~ gestwks, data = births )
> abline( mlin )
```

2. Repeat also the diagnostic plots of this simple model

```
> par( mfrow=c(2,2) )
> plot( mlin )
```

Some deviation from the linear model is apparent.

1.10.2 Fitting a natural cubic spline

A popular approach for flexible modelling is based on natural regression splines, which have more reasonable tail behaviour than polynomial regression.

3. By the following piece of code you can fit a *natural cubic spline* with 5 pre-specified knots to be put at 28, 34, 38, 40 and 43 weeks of gestation, respectively, determining the degree of smoothing.

```
> library(splines)
> mNs5 <- lm( bweight ~ Ns( gestwks, knots = c(28,34,38,40,43)),
+           data = births )
> round( ci.exp( mNs5, Exp=FALSE ), 1)
```

These regression coefficients are even less interpretable than those in the polynomial model.

4. A graphical presentation of the fitted curve together with the confidence and prediction intervals is more informative. As this kind of presentation will be repeated, let us write a short function script to facilitate the task. We utilize function `matshade()` in `Epi`, which creates shaded areas, and function `matlines()` which draws lines joining the pertinent end points over the x -values for which the predictions are computed.

```
> plotFitPredInt <- function( xval, fit, pred, ... )
+ {
+   matshade( xval, fit, lwd=2, alpha=0.2 )
+   matshade( xval, pred, lwd=2, alpha=0.2 )
+   matlines( xval, fit, lty=1, lwd=c(3,2,2), col=c("red","blue","blue") )
+   matlines( xval, pred, lty=1, lwd=c(3,2,2), col=c("red","green","green") )
+ }
```

5. Now, create a vector of x -values and compute the fitted/predicted values as well as the interval limits at these points from the fitted model object utilizing function `predict()`. This function creates a matrix of three columns: (1) fitted/predicted values, (2) lower limits, (3) upper limits

```
> nd <- data.frame(gestwks = seq(24, 45, by = 0.25) )
> fit.Ns5 <- predict( mNs5, newdata=nd, interval="conf" )
> pred.Ns5 <- predict( mNs5, newdata=nd, interval="pred" )
> par(mfrow=c(1,1))
> with( births, plot(bweight ~ gestwks, xlim=c(23, 46),
+                   cex.axis=1.5, cex.lab=1.5 ) )
> plotFitPredInt(xval=nd$gestwks, fit=fit.Ns5, pred=pred.Ns5)
```

Compare this with the 3rd order curve previously fitted (see slide 20 of the lecture). In a natural spline the curve is constrained to be linear beyond the extreme knots.

6. Take a look at the basic diagnostic plots from the spline model.

```
> par(mfrow=c(2,2))
> plot(mNs5)
```

How would you interpret these plots?

The choice of the number of knots and their locations can be quite arbitrary, and the results are often sensitive to these choices.

7. To illustrate arbitrariness and associated problems with specification of knots, you may now fit another natural spline model like the one above but now with 10 knots at the following sequence of points: `seq(25, 43, by = 2)`. Display graphically the results

The behaviour of the curve is really wild for small values of `gestwks`!

1.10.3 Penalized spline model

One way to go around the arbitrariness in the specification of knots is to fit a *penalized spline* model, which imposes a “roughness penalty” on the curve. Even though a big number of knots are initially allowed, the resulting fitted curve will be optimally smooth.

You cannot fit a penalized spline model with `lm()` or `glm()`. Instead, function `gam()` in package `mgcv` can be used for this purpose.

8. You must first load package `mgcv`.
9. When calling `gam()`, the model formula contains expression '`s(X)`' for any explanatory variable `X`, for which you wish to fit a smooth function

```
> library(mgcv)
> mPs <- gam( bweight ~ s(gestwks), data = births)
> summary(mPs)
```

From the output given by `summary()` you find that the estimated intercept is here, too, equal to the overall mean birth weight in the data. The estimated residual variance is given by “Scale est.” or from subobject `sig2` of the fitted `gam` object. Taking square root you will obtain the estimated residual standard deviation: 445.2 g.

```
> mPs$sig2
> sqrt(mPs$sig2)
```

The degrees of freedom in this model are not computed as simply as in previous models, and they typically are not integer-valued. However, the fitted spline seems to consume only a little more degrees of freedom as the 3rd degree polynomial above.

10. As in previous models we shall plot the fitted curve together with 95 % confidence intervals for the mean responses and 95 % prediction intervals for individual responses. Obtaining the prediction intervals from the fitted `gam` object requires a bit more work than with `lm` objects.

```
> pr.Ps <- predict( mPs, newdata=nd, se.fit=TRUE )
> str(pr.Ps) # with se.fit=TRUE, only two columns: fitted value and its SE
> fit.Ps <- cbind(pr.Ps$fit,
+               pr.Ps$fit - 2*pr.Ps$se.fit,
+               pr.Ps$fit + 2*pr.Ps$se.fit)
> pred.Ps <- cbind(pr.Ps$fit, # must add residual variance to se.fit^2
+               pr.Ps$fit - 2*sqrt( pr.Ps$se.fit^2 + mPs$sig2),
+               pr.Ps$fit + 2*sqrt( pr.Ps$se.fit^2 + mPs$sig2))
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim=c(24, 45),
+               cex.axis=1.5, cex.lab=1.5) )
> plotFitPredInt(nd$gestwks, fit.Ps, pred.Ps)
```

The fitted curve is indeed clearly more reasonable than the polynomial.

1.10.4 Testis cancer: Data input and housekeeping

We shall now switch to analyzing the incidence of testis cancer in Denmark during 1943–1998 by age and calendar time or period.

11. Load the data and inspect its structure:

```
> library( Epi )
> data( testisDK )
> str( testisDK )
> summary( testisDK )
> head( testisDK )
```

12. There are nearly 5000 observations from 90 one-year age groups and 54 calendar years. To get a clearer picture of what's going on we do some housekeeping. The age range will be limited to 15–79 years, and age and period are both categorised into 5-year intervals – according to the time-honoured practice in epidemiology.

```
> tdk <- subset(testisDK, A > 14 & A < 80)
> tdk$Age <- cut(tdk$A, br = 5*(3:16), include.lowest=TRUE, right=FALSE)
> nAge <- length(levels(tdk$Age))
> tdk$Per <- cut(tdk$P, br = seq(1943,1998,by=5),
+               include.lowest=TRUE, right=FALSE)
> nPer <- length(levels(tdk$Per))
```

1.10.5 Some descriptive analysis

Computation and tabulation of incidence rates

13. Tabulate numbers of cases and person-years, and compute the incidence rates (per 100,000 y) in each $5 \text{ y} \times 5 \text{ y}$ cell using `stat.table()`

```
> tab <- stat.table( index = list(Age, Per),
+                   contents = list(D = sum(D),
+                                   Y = sum(Y/1000),
+                                   rate = ratio(D, Y, 10^5) ),
+                   margins = TRUE,
+                   data = tdk )
> print(tab, digits=c(sum=0, ratio=1))
```

Look at the incidence rates in the column margin and in the row margin. In which age group is the marginal age-specific rate highest? Do the period-specific marginal rates have any trend over time?

14. From the saved table object `tab` you can plot an age-incidence curve for each period separately, after you have checked the structure of the table, so that you know the relevant dimensions in it. There is a function `rateplot()` in `Epi` that does default plotting of tables of rates (see the help page of `rateplot`)

```
> str(tab)
> par(mfrow=c(1,1))
> rateplot( rates=tab[3, 1:nAge, 1:nPer], which="ap", ylim=c(1,30),
+           age=seq(15, 75, 5), per=seq(1943, 1993, 5),
+           col=heat.colors(16), ann=TRUE )
```

Is there any common pattern in the age-incidence curves across the periods?

1.10.6 Age and period as categorical factors

We shall first fit a Poisson regression model with log link on age and period model in the traditional way, in which both factors are treated as categorical. The model is additive on the log-rate scale. It is useful to scale the person-years to be expressed in 10^5 y.

```
15. > tdk$Y <- tdk$Y/100000
> mCat <- glm( cbind(D,Y) ~ Age + Per,
+             family=poisreg(link=log), data= tdk )
> round( ci.exp( mCat ), 2)
```

What do the estimated rate ratios tell about the age and period effects?

16. A graphical inspection of point estimates and confidence intervals can be obtained as follows. In the beginning it is useful to define shorthands for the pertinent mid-age and mid-period values of the different intervals

```
> aMid <- seq(17.5, 77.5, by = 5)
> pMid <- seq(1945, 1995, by = 5)
> par(mfrow=c(1,2))
> plot( c(15,80), c(0.6, 6), type="n", log="y",
+       cex.lab = 1.5, cex.axis = 1.5,
+       xlab = "Age (years)", ylab = "Rate ratio")
> lines( aMid, c( 1, ci.exp(mCat)[2:13, 1] ), type = "o", pch = 16 )
> segments( aMid[-1], ci.exp(mCat)[2:13, 2],
+          aMid[-1], ci.exp(mCat)[2:13, 3] )
> plot( c(1943,1998), c(0.6, 6), type="n", log="y",
+       cex.lab = 1.5, cex.axis = 1.5,
+       xlab = "Calendar year - 1900", ylab = "Rate ratio")
> lines( pMid, c( 1, ci.exp(mCat)[14:23, 1] ), type = 'o', pch = 16 )
> segments( pMid[-1], ci.exp(mCat)[14:23, 2],
+          pMid[-1], ci.exp(mCat)[14:23, 3] )
```

17. In the fitted model the reference category for each factor was the first one. As age is the dominating factor, it may be more informative to remove the intercept from the model. As a consequence the age effects describe fitted rates at the reference level of the period factor. For the latter one could choose the middle period 1968-72.

```
> tdk$Per70 <- Relevel(tdk$Per, ref = 6)
> mCat2 <- glm( cbind(D,Y) ~ -1 + Age +Per70,
+             family=poisreg(link=log), data= tdk )
> round( ci.exp( mCat2 ), 2)
```

We shall plot just the point estimates from the latter model

```
> par(mfrow=c(1,2))
> plot( c(15,80), c(2, 20), type="n", log="y", cex.lab = 1.5, cex.axis = 1.5,
+       xlab = "Age (years)", ylab = "Incidence rate (per 100000 y)")
> lines( aMid, c(ci.exp(mCat2)[1:13, 1] ), type = "o", pch = 16)
> plot( c(1943,1998), c(0.4, 2), type="n", log="y",
+       cex.lab = 1.5, cex.axis = 1.5,
+       xlab = "Calendar year", ylab = "Rate ratio")
> lines( pMid, c(ci.exp(mCat2)[14:18, 1], 1, ci.exp(mCat2)[19:23, 1]),
+       type = "o", pch = 16 )
> abline(h=1, col="gray")
```

1.10.7 Generalized additive model with penalized splines

It is obvious that the age effect on the log-rate scale is highly non-linear. Yet, it is less clear whether the true period effect deviates from linearity. Nevertheless, there are good indications to try fitting smooth continuous functions for both.

18. As the next task we fit a generalized additive model for the log-rate on continuous age and period applying penalized splines with default settings of function `gam()` in package `mgcv`. In this fitting an “optimal” value for the penalty parameter is chosen based on an AIC-like criterion known as UBRE.

```
> library(mgcv)
> mPen <- gam( cbind(D, Y) ~ s(A) + s(P),
+             family = poisreg(link=log), data = tdk)
> summary(mPen)
```

The summary is quite brief, and the only estimated coefficient is the intercept, which sets the baseline level for the log-rates, against which the relative age effects and period effects will be contrasted. On the rate scale the baseline level 5.53 per 100000 y is obtained by `exp(1.7096)`.

19. See also the default plot for the fitted curves (solid lines) describing the age and the period effects which are interpreted as contrasts to the baseline level on the log-rate scale.

```
> par(mfrow=c(1,2))
> plot(mPen, seWithMean=TRUE)
```

The dashed lines describe the 95 % confidence band for the pertinent curve. One could get the impression that year 1968 would be some kind of reference value for the period effect, like period 1968-72 chosen as the reference in the categorical model previously fitted. This is not the case, however, because `gam()` by default parametrizes the spline effects such that the reference level, at which the spline effect is nominally zero, is the overall “grand mean” value of the log-rate in the data. This corresponds to the principle of *sum contrasts* (`contr.sum`) for categorical explanatory factors.

From the summary you will also find that the degrees of freedom value required for the age effect is nearly the same as the default dimension $k - 1 = 9$ of the part of the model matrix (or basis) initially allocated for each smooth function. (Here k refers to the relevant argument that determines the basis dimension when specifying a smooth term by `s()` in the model formula). On the other hand the period effect takes just about 3 df.

20. It is a good idea to do some diagnostic checking of the fitted model

```
> par(mfrow=c(2,2))
> gam.check(mPen)
```

The four diagnostic plots are analogous to some of those used in the context of linear models for Gaussian responses, but not all of them may be as easy to interpret. – Pay attention to the note given in the printed output about the value of `k`.

21. Let us refit the model but now with an increased k for age:

```
> mPen2 <- gam( cbind(D,Y) ~ s(A, k=20) + s(P),
+               family = poisreg(link=log), data = tdk)
> summary(mPen2)
> par(mfrow=c(2,2))
> gam.check(mPen2)
```

With this choice of k the df value for age became about 11, which is well below $k - 1 = 19$. Let us plot the fitted curves from this fitting, too

```
> par( mfrow=c(1,2) )
> plot( mPen2, seWithMean=TRUE )
> abline( v=1968, h=0, lty=3 )
```

There does not seem to have happened any essential changes from the previously fitted curves, so maybe 8 df could, after all, be quite enough for the age effect.

22. Graphical presentation of the effects using `plot.gam()` can be improved. For instance, we may present the age effect to describe the “mean” incidence rates by age, averaged over the whole time span of 54 years. This is obtained by adding the estimated intercept to the estimated smooth curve for the age effect and showing the antilogarithms of the ordinates of the curve. For that purpose we need to extract the intercept and modify the labels of the y -axis accordingly. The estimated period curve can also be expressed in terms of relative incidence rates in relation to the fitted baseline rate, as determined by the model intercept.

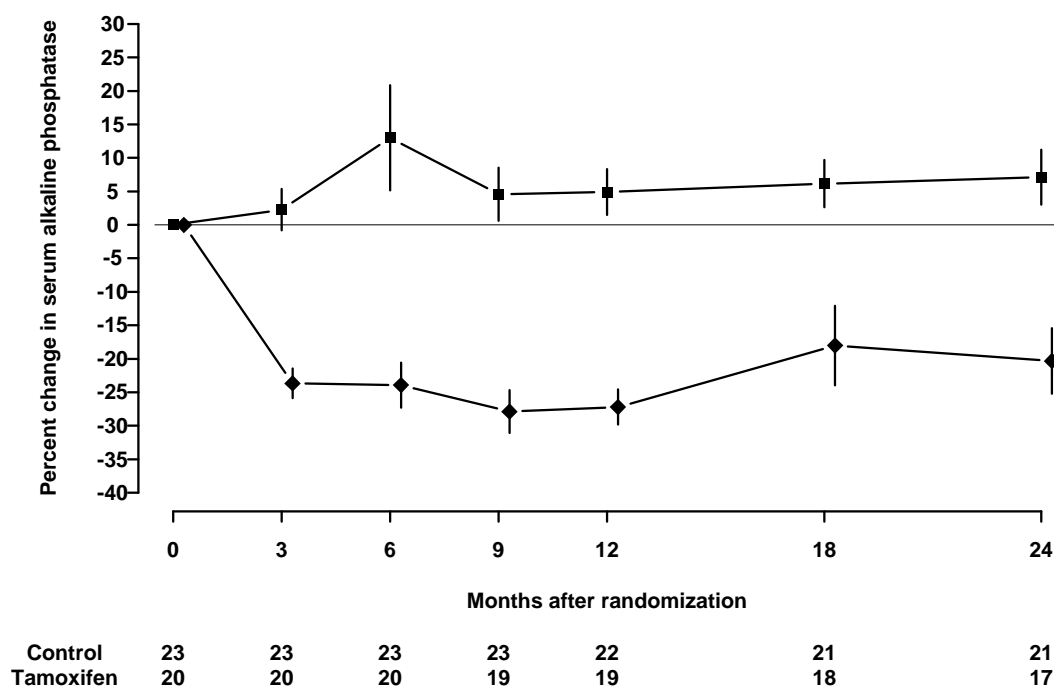
```
> par( mfrow=c(1,2) )
> icpt <- coef(mPen2)[1] # estimated intercept
> plot( mPen2, seWithMean=TRUE, select=1, rug=FALSE,
+       yaxt="n", ylim= c(log(1),log(20)) - icpt,
+       xlab="Age (y)", ylab="Mean rate (/100000 y)" )
> axis(2, at = log( c(1, 2, 5, 10, 20)) - icpt, labels=c(1, 2, 5, 10, 20) )
> plot( mPen2, seWithMean=TRUE, select=2, rug=FALSE,
+       yaxt="n", ylim=c( log(0.4), log(2) ),
+       xlab="Calendar year", ylab="Relative rate")
> axis(2, at=log( c(0.5, 0.75, 1, 1.5, 2)), labels = c(0.5, 0.75, 1, 1.5, 2))
> abline( v=1968, h=0, lty=3 )
```

One could continue the analysis of these data by fitting an age-cohort model as an alternative to the age-period model, as well as an age-cohort-period model.

There will also be some extras added in the solution part of this exercise.

1.11 Graphics meccano

The plot below is from a randomized study of the effect of Tamoxifen treatment on bone mineral metabolism, in a group of patients who were treated for breast cancer.



The data are available in the file `alkfos.csv` (using comma as separator, so `read.csv` will read it).

```
> alkfos <- read.csv("./data/alkfos.csv") # change filename as needed
```

The purpose of this exercise is to show you how to build a similar graph using base graphics in R. This will take you through a number of fundamental techniques. The exercise will also walk you through creating the graph using `ggplot2`.

To get started, run the code in the housekeeping script `alkfos-house.r`. You probably should not study the code in too much detail at this point. The script create the following objects in your workspace.

- `times`, a vector of length 7 giving the observation times
- `means`, a 2×7 matrix giving the mean percentage change at each time point. Each group has its own row.
- `sems`, a 2×7 matrix giving standard errors of the means, used to create the error bars.
- `available`, a 2×7 matrix giving the number of participants still available

Use the `objects()` to see the objects created function to see them.

1.11.1 Base graphics

Now we start building the plot. It is important that you use some form of script to hold the R code since you will frequently have to modify and rerun previously entered code.

1. First, plot the means for group 1 (i.e. `means[1,]`) against `times`, using `type="b"` (look up what this does)
2. Then *add* a similar curve for group 2 to the plot using `points` or `lines`. Notice that the new points are below the y scale of the plot, so you need to revise the initial plot by setting a suitable `ylim` value.
3. Add the error bars using `segments`. (You can calculate the endpoints using `upper <- means + sems` etc.). You may have to adjust the `ylim` again.
4. Add the horizontal line at $y = 0$ using `abline`
5. Use `xlab` and `ylab` in the initial `plot` call to give better axis labels.
6. We need a nonstandard x axis. Use `xaxt="n"` to avoid plotting it at first, then add a custom axis with `axis`
7. The counts below the x axis can be added using `mtext` on lines 5 and 6 below the bottom of the plot, but you need to make room for the extra lines. Use `par(mar=.1 + c(8,4,4,2))` *before* plotting anything to achieve this.

You now have quite a good reconstruction of the original plot. There are some additional steps you can take to reproduce the published plot exactly. These are advanced exercises so feel free to come back to them later.

8. It is not too important here (it was for some other variables in the study), but the S-PLUS plot has the points for the second group offset horizontally by a small amount (.25) to prevent overlap. Redo the plot with this modification.
9. Further things to fiddle with: Get rid of the bounding box. Add Control/Tamoxifen labels to the lines of counts. Perhaps use different plotting symbols. Rotate the y axis values. Modify the line widths or line styles.
10. Finally, try plotting to the `pdf()` device and view the results using a PDF viewer (*e.g.* Adobe Acrobat Reader). You may need to change the `pointsize` option and/or the plot dimensions for optimal appearance. You might also try saving the plot as a metafile and include it in a Word document.

1.11.2 Using ggplot2

The housekeeping script `alkfos-house.r` also creates a data frame `ggdata` containing the variables in long format. The code for generating the data frame is shown below, but you do not need to repeat it if you have run the script.

```
> ggdata <- data.frame(
+   times = rep(times, 2),
+   means = c(means[1,], means[2,]),
+   sds = c(sds[1,], sds[2,]),
+   available = c(available[1,], available[2,]),
+   treat = rep(c("placebo", "tamoxifen"), each=7)
+ )
> ggdata <- transform(ggdata, sems = sds/sqrt(available))
```

To create a first approximation to the plot in **ggplot2** we use the **qplot** function (short for “quick plot”). First you must install the **ggplot2** package from CRAN and then load it:

```
> library(ggplot2)
> qplot(x=times, y=means, group=treat, geom=c("point", "line") , data=ggdata)
```

The first arguments to **qplot** are called “aesthetics” in the grammar of graphics. Here we want to plot **y=means** by **x=times** grouped by **group=treat**. The aesthetics are used by the “geometries”, which are specified with the **geom** argument. Here we want to plot both points and lines. The **data** argument tells **qplot** to get the aesthetics from the data frame **ggdata**.

To add the error bars, we add a new geometry “**linrange**” which uses the aesthetics **ymin** and **ymax**

```
> p <- qplot(x=times, y=means, group=treat,
+           ymin=means-sems, ymax=means+sems,
+           yintercept=0, geom=c("point", "line", "linrange"),
+           data=ggdata)
> print(p)
```

In this case we are saving the output of **qplot** to an R object **p**. This means the plot will not appear automatically when we call **qplot**. Instead, we must explicitly print it.

Note how the y axes are automatically adjusted to include the error bars. This is because they are included in the call to **qplot** and not added later (as was the case with base graphics).

It remains to give informative axis labels and put the right tick marks on the x-axis. This is done by adding scales to the plot

```
> p <- p +
+   scale_x_continuous(name="Months after randomization",
+                     breaks=ggdata$times) +
+   scale_y_continuous(name="% change in alkaline phosphatase")
> print(p)
```

We can also change the look and feel of the plot by adding a theme (in this case the black and white theme).

```
> p + theme_bw()
```

As an alternative to **qplot**, we can use the **ggplot** function to define the data and the common aesthetics, then add the geometries with separate function calls. All the grobs (*graphical objects*) created by these function calls are combined with the **+** operator:

```
> p <- ggplot(data=ggdata,
+           aes(x=times, y=means, ymin=means-sems, ymax=means+sems,
+             group=treat)) +
+   geom_point() +
+   geom_line() +
```

```
+ geom_linerange() +
+ geom_hline(yintercept=0, colour="darkgrey") +
+ scale_x_continuous(breaks=ggdata$times) +
+ scale_y_continuous(breaks=seq(-35,25,5))
> print(p)
```

This call adds another geometry “hline” which uses the aesthetic `yintercept` to add a horizontal line at 0 on the y-axis. Note that this alternate syntax allows each geometry to have its own aesthetics: here we draw the horizontal line in darkgrey instead of the default black.

1.11.3 Grid graphics

As a final, advanced topic, this subsection shows how viewports from the `grid` package may be used to display the plot and the table in the same graph. First we create a text table:

```
> tab <- ggplot(data=ggdata, aes(x=times, y=treat, label=available)) +
+   geom_text(size=3) + xlab(NULL) + ylab(NULL) +
+   scale_x_continuous(breaks=NULL)
> tab
```

Then we create a layout that will contain the graph above the table. Most of the space is taken by the graph. The `grid.show.layout` allows you to preview the layout.

```
> library(grid)
> Layout <- grid.layout(nrow = 2, ncol = 1, heights = unit(c(2, 0.25),
+   c("null", "null")))
> grid.show.layout(Layout)
```

The units are relative (“null”) units. You can specify exact sizes in centimetres, inches, or lines if you prefer.

We then print the graph and the table in the appropriate viewports

```
> grid.newpage() #Clear the page
> pushViewport(viewport(layout=Layout))
> print(p, vp=viewport(layout.pos.row=1, layout.pos.col=1))
> print(tab, vp=viewport(layout.pos.row=2, layout.pos.col=1))
```

Notice that the left margins do not match. One way to get the margins to match is to use the `plot_grid` function from the `cowplot` package.

```
> library(cowplot)
> plot_grid(p, tab, align="v", ncol=1, nrow=2, rel_heights=c(5,1))
```

The `cowplot` package has a theme that is useful for publications. It is a black and white theme with no grid:

```
> theme_set(theme_cowplot())
> plot_grid(p, tab, align="v", ncol=1, nrow=2, rel_heights=c(5,1))
```

The `theme_set` function changes the default `ggplot2` theme so that all subsequent displays will use the given theme.

1.12 Survival analysis: Oral cancer patients

1.12.1 Description of the data

File `oralca2.txt`, that you may access from a url address to be given in the practical, contains data from 338 patients having an oral squamous cell carcinoma diagnosed and treated in one tertiary level oncological clinic in Finland since 1985, followed-up for mortality until 31 December 2008. The dataset contains the following variables:

`sex` = sex, a factor with categories 1 = "Female", 2 = "Male",
`age` = age (years) at the date of diagnosing the cancer,
`stage` = TNM stage of the tumour (factor): 1 = "I", ..., 4 = "IV", 5 = "unkn",
`time` = follow-up time (in years) since diagnosis until death or censoring,
`event` = event ending the follow-up (numeric):
0 = censoring alive, 1 = death from oral cancer, 2 = death from other causes.

1.12.2 Loading the packages and the data

11. Load the R packages `Epi`, `mstate`, and `survival` needed in this exercise.

```
> library(Epi)
> library(popEpi)
> library(data.table)
> library(knitr)
> library(survival)
```

12. Read the datafile `oralca2.txt` from a website, whose precise address will be given in the practical, into an R data frame named `orca`. Look at the head, structure and the summary of the data frame. Using function `table()` count the numbers of censorings as well as deaths from oral cancer and other causes, respectively, from the `event` variable.

```
> orca <- read.table("pracs/data/oralca2.txt", header=T)
> head(orca) ; str(orca) ; summary(orca)
```

1.12.3 Total mortality: Kaplan–Meier analyses

1. We start our analysis of total mortality pooling the two causes of death into a single outcome. First, construct a *survival object* `orca$suob` from the event variable and the follow-up time using function `Surv()`. Look at the structure and summary of `orca$suob`.

```
> orca$suob <- Surv(orca$time, 1*(orca$event > 0) )
> str(orca$suob)
> summary(orca$suob)
```

2. Create a `survfit` object `s.all`, which does the default calculations for a Kaplan–Meier analysis of the overall (marginal) survival curve.

```
> s.all <- survfit(suob ~ 1, data=orca)
```

See the structure of this object and apply `print()` method on it, too. Look at the results; what do you find?

```
> s.all
> str(s.all)
```

3. The `summary` method for a `survfit` object would return a lengthy life table. However, the `plot` method with default arguments offers the Kaplan–Meier curve for a conventional illustration of the survival experience in the whole patient group. Alternatively, instead of graphing survival proportions, one can draw a curve describing their complements: the cumulative mortality proportions. This curve is drawn together with the survival curve as the result of the second command line below.

```
> plot(s.all)
> lines(s.all, fun = "event", mark.time=F, conf.int=F)
```

The effect of option `mark.time=F` is to omit marking the times when censorings occurred.

1.12.4 Total mortality by stage

Tumour stage is an important prognostic factor in cancer survival studies.

1. Plot separate cumulative mortality curves for the different stage groups marking them with different colours, the order which you may define yourself. Also find the median survival time for each stage.

```
> s.stg <- survfit(suob ~ stage, data= orca)
> col5 <- c("green", "blue", "black", "red", "gray")
> plot(s.stg, col= col5, fun="event", mark.time=F )
> s.stg
```

2. Create now two parallel plots of which the first one describes the cumulative hazards and the second one graphs the log-cumulative hazards against log-time for the different stages. Compare the two presentations with each other and with the one in the previous item.

```
> par(mfrow=c(1,2))
> plot(s.stg, col= col5, fun="cumhaz", main="cum. hazards" )
> plot(s.stg, col= col5, fun="cloglog", main = "cloglog: log cum.haz" )
```

3. If the survival times were *exponentially* distributed in a given (sub)population the corresponding cloglog-curve should follow an approximately linear pattern. Could this be the case here in the different stages?
4. Also, if the survival distributions of the different subpopulations would obey the *proportional hazards* model, the vertical distance between the cloglog-curves should be approximately constant over the time axis. Do these curves indicate serious deviation from the proportional hazards assumption?

5. In the lecture handouts (p. 34, 37) it was observed that the crude contrast between males and females in total mortality appears unclear, but the age-adjustment in the Cox model provided a more expected hazard ratio estimate. We shall examine the confounding by age somewhat closer. First categorize the continuous age variable into, say, three categories by function `cut()` using suitable breakpoints, like 55 and 75 years, and cross-tabulate sex and age group:

```
> orca$agegr <- cut(orca$age, br=c(0,55,75, 95))
> stat.table( list( sex, agegr), list( count(), percent(agegr) ),
+           margins=T, data = orca )
```

Male patients are clearly younger than females in these data.

Now, plot Kaplan–Meier curves jointly classified by sex and age.

```
> s.agrx <- survfit(suob ~ agegr + sex, data=orca)
> par(mfrow=c(1,1))
> plot(s.agrx, fun="event", mark.time=F, xlim = c(0,15),
+      col=rep(c("red", "blue"),3), lty=c(2,2, 1,1, 5,5))
```

In each ageband the mortality curve for males is on a higher level than that for females.

1.12.5 Event-specific cumulative mortality curves

We move on to analysing cumulative mortalities for the two causes of death separately, first overall and then by prognostic factors.

1. Use the `survfit`-function in `survival` package with option `type="mstate"`.

```
> library(survival)
> cif1 <- survfit( Surv( time, event, type="mstate") ~ 1,
+               data = orca)
> str(cif1)
```

2. One could apply here the `plot` method of the `survfit` object to plot the cumulative incidences for each cause. However, we suggest that you use instead a simple function `plotCIF()` found in the `Epi` package. The main arguments are

`data` = data frame created by function `survfit()`, (1.1)

`event` = indicator for the event: values 1 or 2. (1.2)

Other arguments are like in the ordinary `plot()` function.

3. Draw two parallel plots describing the overall cumulative incidence curves for both causes of death

```
> par(mfrow=c(1,2))
> plotCIF(cif1, 1, main = "Cancer death")
> plotCIF(cif1, 2, main= "Other deaths")
```

4. Compute the estimated cumulative incidences by stage for both causes of death. Now you have to add variable `stage` to `survfit`-function.

See the structure of the resulting object, in which you should observe `strata` variable containing the stage grouping variable. Plot the pertinent curves in two parallel graphs. Cut the *y*-axis for a more efficient graphical presentation

```
> col5 <- c("green", "blue", "black", "red", "gray")
> cif2 <- survfit( Surv( time, event, type="mstate") ~ stage,
+               data = orca)
> str(cif2)
> par(mfrow=c(1,2))
> plotCIF(cif2, 1, main = "Cancer death by stage",
+         col = col5, ylim = c(0, 0.7) )
> plotCIF(cif2, 2, main= "Other deaths by stage",
+         col=col5, ylim = c(0, 0.7) )
```

Compare the two plots. What would you conclude about the effect of stage on the two causes of death?

5. Using another function `stackedCIF()` in `Epi` you can put the two cumulative incidence curves in one graph but stacked upon one another such that the lower curve is for the cancer deaths and the upper curve is for total mortality, and the vertical difference between the two curves describes the cumulative mortality from other causes. You can also add some colours for the different zones:

```
> par(mfrow=c(1,1))
> stackedCIF(cif1, colour = c("gray70", "gray85"))
```

1.12.6 Regression modelling of overall mortality.

1. Fit the semiparametric proportional hazards regression model, a.k.a. the Cox model, on all deaths including sex, age and stage as covariates. Use function `coxph()` in package `survival`. It is often useful to center and scale continuous covariates like `age` here. The estimated rate ratios and their confidence intervals can also here be displayed by applying `ci.lin()` on the fitted model object.

```
> options(show.signif.stars = F)
> m1 <- coxph(suob ~ sex + I((age-65)/10) + stage, data= orca)
> summary( m1 )
> round( ci.exp(m1 ), 4 )
```

Look at the results. What are the main findings?

2. Check whether the data are sufficiently consistent with the assumption of proportional hazards with respect to each of the variables separately as well as globally, using the `cox.zph()` function.

```
> cox.zph(m1)
```


3. No evidence against proportionality assumption could apparently be found. Moreover, no difference can be observed between stages I and II in the estimates. On the other hand, the group with stage unknown is a complex mixture of patients from various true stages. Therefore, it may be prudent to exclude these subjects from the data and to pool the first two stage groups into one. After that fit a model in the reduced data with the new stage variable.

```
> orca2 <- subset(orca, stage != "unkn")
> orca2$st3 <- Relevel( orca2$stage, list(1:2, 3, 4:5) )
> levels(orca2$st3) = c("I-II", "III", "IV")
> m2 <- update(m1, . ~ . - stage + st3, data=orca2 )
> round( ci.exp(m2 ), 4)
```

4. Plot the predicted cumulative mortality curves by stage, jointly stratified by sex and age, focusing only on 40 and 80 year old patients, respectively, based on the fitted model m2. You need to create a new artificial data frame containing the desired values for the covariates.

```
> newd <- data.frame( sex = c( rep("Male", 6), rep("Female", 6) ),
+                      age = rep( c( rep(40, 3), rep(80, 3) ), 2 ),
+                      st3 = rep( levels(orca2$st3), 4) )
> newd
> col3 <- c("green", "black", "red")
> par(mfrow=c(1,2))
> plot( survfit(m2, newdata= subset(newd, sex=="Male" & age==40)),
+       col=col3, fun="event", mark.time=F)
> lines( survfit(m2, newdata= subset(newd, sex=="Female" & age==40)),
+       col= col3, fun="event", lty = 2, mark.time=F)
> plot( survfit(m2, newdata= subset(newd, sex=="Male" & age==80)),
+       ylim = c(0,1), col= col3, fun="event", mark.time=F)
> lines( survfit(m2, newdata= subset(newd, sex=="Female" & age==80)),
+       col=col3, fun="event", lty=2, mark.time=F)
>
```

1.12.7 Modelling event-specific hazards and hazards of the subdistribution

1. Fit the Cox model for the cause-specific hazard of cancer deaths with the same covariates as above. In this case only cancer deaths are counted as events and deaths from other causes are included into censorings.

```
> m2haz1 <- coxph( Surv( time, event==1) ~ sex + I((age-65)/10) + st3 , data=orca2 )
> round( ci.exp(m2haz1 ), 4)
> cox.zph(m2haz1)
```

Compare the results with those of model m2. What are the major differences?

2. Fit a similar model for deaths from other causes and compare the results.

```
> m2haz2 <- coxph( Surv( time, event==2) ~ sex + I((age-65)/10) + st3 , data=orca2 )
> round( ci.exp(m2haz2 ), 4)
> cox.zph(m2haz2)
```

3. Finally, fit the Fine–Gray model for the hazard of the subdistribution for cancer deaths with the same covariates as above. For this you have to first load package `cmprsk`, containing the necessary function `crr()`, and attach the data frame.

```
> library(cmprsk)
> attach(orca2)
> m2fg1 <- crr(time, event, cov1 = model.matrix(m2), failcode=1)
> summary(m2fg1, Exp=T)
```

Compare the results with those of model `m2` and `m2haz1`.

4. Fit a similar model for deaths from other causes and compare the results.

```
> m2fg2 <- crr(time, event, cov1 = model.matrix(m2), failcode=2)
> summary(m2fg2, Exp=T)
```

1.12.8 Lexis object with multi-state set-up

Before entering to analyses of cause-specific mortality it might be instructive to apply some Lexis tools to illustrate the competing-risks set-up. More detailed explanation of these tools will be given by Bendix in this afternoon.

1. Form a `Lexis` object from the data frame and print a summary of it. We shall name the main (and only) time axis in this object as `stime`.

```
> orca.lex <- Lexis(exit = list(stime = time),
+                 exit.status = factor(event,
+   labels = c("Alive", "Oral ca. death", "Other death")),
+                 data = orca)
> summary(orca.lex)
```

2. Draw a box diagram of the two-state set-up of competing transitions. Run first the following command line

```
boxes( orca.lex )
```

Now, move the cursor to the point in the graphics window, at which you wish to put the box for “Alive”, and click. Next, move the cursor to the point at which you wish to have the box for “Oral ca. death”, and click. Finally, do the same with the box for “Other death”. If you are not happy with the outcome, run the command line again and repeat the necessary mouse moves and clicks.

1.12.9 Poisson regression as an alternative to Cox model

It can be shown that the Cox model with an unspecified form for the baseline hazard $\lambda_0(t)$ is mathematically equivalent to the following kind of Poisson regression model. Time is treated as a categorical factor with a dense division of the time axis into disjoint intervals or *timebands* such that only one outcome event occurs in each timeband. The model formula contains this time factor plus the desired explanatory terms.

A sufficient division of time axis is obtained by first setting the break points between adjacent timebands to be those time points at which an outcome event has been observed to occur. Then, the pertinent `lexis` object is created and after that it will be split according to those breakpoints. Finally, the Poisson regression model is fitted on the splitted `lexis` object using function `glm()` with appropriate specifications.

We shall now demonstrate the numerical equivalence of the Cox model `m2haz1` for oral cancer mortality that was fitted above, and the corresponding Poisson regression.

1. First we form the necessary `lexis` object by just taking the relevant subset of the already available `orca.lex` object. Upon that the three-level stage factor `st3` is created as above.

```
> orca2.lex <- subset(orca.lex, stage != "unkn" )
> orca2.lex$st3 <- Relevel( orca2$stage, list(1:2, 3, 4:5) )
> levels(orca2.lex$st3) = c("I-II", "III", "IV")
```

Then, the break points of time axis are taken from the sorted event times, and the `lexis` object is split by those breakpoints. The `timeband` factor is defined according to the splitted survival times stored in variable `stime`.

```
> cuts <- sort(orca2$time[orca2$event==1])
> orca2.spl <- splitLexis( orca2.lex, br = cuts, time.scale="stime" )
> orca2.spl$timeband <- as.factor(orca2.spl$stime)
```

As a result we now have an expanded `lexis` object in which each subject has several rows; as many rows as there are such timebands during which he/she is still at risk. The outcome status `lex.Xst` has value 0 in all those timebands, over which the subject stays alive, but assumes the value 1 or 2 at his/her last interval ending at the time of death. – See now the structure of the splitted object.

```
> str(orca2.spl)
> orca2.spl[ 1:20, ]
```

2. We are ready to fit the desired Poisson model for oral cancer death as the outcome. The splitted person-years are contained in `lex.dur`, and the explanatory variables are the same as in model `m2haz1`. – This fitting may take some time ...

```
> m2pois1 <- glm( 1*(lex.Xst=="Oral ca. death") ~
+               -1 + timeband + sex + I((age-65)/10) + st3,
+               family=poisson, offset = log(lex.dur), data = orca2.spl)
```

We shall display the estimation results graphically for the baseline hazard (per 1000 person-years) and numerically for the rate ratios associated with the covariates. Before doing that it is useful to count the length `ntb` of the block occupied by baseline hazard in the whole vector of estimated parameters. However, owing to how the splitting to timebands was done, the last regression coefficient is necessarily zero and better be omitted when displaying the results. Also, as each timeband is quantitatively named according to its leftmost point, it is good to compute the midpoint values `tbmid` for the timebands

```

> tb <- as.numeric(levels(orca2.spl$timeband)) ; ntb <- length(tb)
> tbmid <- (tb[-ntb] + tb[-1])/2 # midpoints of the intervals
> round( ci.exp(m2pois1 ), 3)
> par(mfrow=c(1,1))
> plot( tbmid, 1000*exp(coef(m2pois1)[1:(ntb-1)]),
+       ylim=c(5,3000), log = "xy", type = "l")

```

Compare the regression coefficients and their error margins to those model `m2haz1`. Do you find any differences? How does the estimated baseline hazard look like?

3. The estimated baseline looks quite ragged when based on 71 separate parameters. A smoothed estimate may be obtained by spline modelling using the tools contained in package `splines` (see the practical of Saturday 25 May afternoon). With the following code you will be able to fit a reasonable spline model for the baseline hazard and draw the estimated curve (together with a band of the 95% confidence limits about the fitted values). From the same model you should also obtain quite familiar results for the rate ratios of interest.

```

> library(splines)
> m2pspli <- update(m2pois1, . ~ ns(stime, df = 6, intercept = F) +
+   sex + I((age-65)/10) + st3)
> round( ci.exp( m2pspli ), 3)
> news <- data.frame( stime = seq(0,25, length=301), lex.dur = 1000, sex = "Female",
+   age = 65, st3 = "I-II")
> blhaz <- predict(m2pspli, newdata = news, se.fit = T, type = "link")
> blh95 <- cbind(blhaz$fit, blhaz$se.fit) %*% ci.mat()
> par(mfrow=c(1,1))
> matplot( news$stime, exp(blh95), type = "l", lty = c(1,1,1), lwd = c(2,1,1) ,
+   col = rep("black", 3), log = "xy", ylim = c(5,3000) )

```

1.13 Time-splitting, time-scales and SMR

This exercise is about mortality among Danish Diabetes patients. It is based on the dataset `DMlate`, a random sample of 10,000 patients from the Danish Diabetes Register (scrambled dates), all with date of diagnosis after 1994.

1. First load the data and take a look at the data:

```
library( Epi)
library(popEpi)
library( mgcv)
library(tidyverse)
sessionInfo()
data( DMlate)
str( DMlate)
```

You can get a more detailed explanation of the data by referring to the help page:

```
?DMlate
```

2. Set up the dataset as a `Lexis` object with age, calendar time and duration of diabetes as timescales, and date of death as event. Make sure that you know what each of the arguments to `Lexis` mean:

```
LL <- Lexis(entry = list(A = dodm-dobth,
                        P = dodm,
                        dur = 0),
            exit = list(P = dox),
            exit.status = factor(!is.na(dodth),
                                labels = c("Alive", "Dead")),
            data = DMlate)
```

Take a look at the first few lines of the resulting dataset, for example using `head()`.

3. Get an overview of the mortality by using `stat.table` to tabulate no. deaths, person-years (`lex.dur`) and the crude mortality rate by sex. Try:

```
stat.table(sex,
            list(D = sum(lex.Xst == "Dead"),
                 Y = sum(lex.dur),
                 rate = ratio(lex.Xst == "Dead", lex.dur, 1000)),
            margins = TRUE,
            data = LL)
```

4. If we want to assess how mortality depends on age, calendar time and duration or how it relates to population mortality, we should in principle split the follow-up along all three time scales. In practice it is sufficient to split it along one of the time-scales and then use the value of each of the time-scales at the left endpoint of the intervals. Use `splitLexis` (or `splitMulti` from the `popEpi` package) to split the follow-up along the age-axis in suitable intervals (here set to 1/2 year, but really immaterial as long as it is small):

```
SL <- splitLexis(LL, breaks = seq(0,125,1/2), time.scale = "A")
summary(SL)
```

How many records are now in the dataset? How many person-years? Compare to the original `Lexis`-dataset.

Age-specific mortality

5. Now estimate age-specific mortality curves for men and women separately, using splines as implemented in `gam`. We use `k = 20` to be sure to catch any irregularities by age.

```
r.m <- gam(cbind(lex.Xst == "Dead", lex.dur) ~ s(A, k = 20),
          family = poisreg,
          data = subset(SL, sex == "M"))
gam.check(r.m)
```

Make sure you understand all the components on this modeling statement. Fit the same model for women. There is a convenient wrapper for this, exploiting the `Lexis` structure of data, but which does not have an update

```
r.m <- gam.Lexis(subset(SL, sex == "M"), ~ s(A, k = 20))
r.f <- gam.Lexis(subset(SL, sex == "F"), ~ s(A, k = 20))
gam.check(r.m)
gam.check(r.f)
```

6. Now, extract the estimated rates by using the wrapper function `ci.pred` that computes predicted rates and confidence limits for these. However, when using the `glm.Lexis` or `gam.Lexis` we avoid this; they rely on the `poisreg` family that will return the rates in the (inverse) units in which the person-years were given; that is the units of `lex.dur`.

```
nd <- data.frame(A = seq(20,90,0.5))
p.m <- ci.pred(r.m, newdata = nd)
p.f <- ci.pred(r.f, newdata = nd)
str(p.m)
```

7. Plot the predicted rates for men and women together - using for example `matplot` or `matshade`.

```
p.f <- ci.pred(r.f, newdata = nd)
matplot(nd$A, cbind(p.m,p.f) * 1000,
        type = "l", col = rep(c("blue","red"),each = 3), lwd = c(3,1,1), lty = 1,
        log = "y", xlab = "Age", ylab = "Mortality of DM ptt per 1000 PY")
```

Further time scales: period and duration

8. We now want to model the mortality rates among diabetes patients also including current date and duration of diabetes, using penalized splines. Use the argument `bs = "cr"` to `s()` to get cubic splines instead of thin plate ("`tp`") splines which is the default. Check if you have a reasonable fit using `gam.check`.

```
Mtp <- gam((lex.Xst == "Dead") ~ s( A, bs = "cr", k = 10) +
                               s( P, bs = "cr", k = 10) +
                               s(dur, bs = "cr", k = 10),
          offset = log(lex.dur),
          family = poisson,
          data = subset(SL, sex == "M"))
```

An easier specification of the model exploits the `Lexis` class of the dataset, try:

```
Mcr <- gam.Lexis(subset(SL, sex == "M"),
  ~ s( A, bs = "cr", k = 10) +
    s( P, bs = "cr", k = 10) +
    s(dur, bs = "cr", k = 10))
summary(Mcr)
gam.check(Mcr)
```

Fit the same model for women as well. Are the models reasonably fitting?

9. Plot the estimated effects, using the default plot method for `gam` objects. Remember that there are three effects estimated, so it is useful set up a multi-panel display, and for the sake of comparability to set `ylim` to the same for men and women:

```
par(mfrow = c(2,3))
plot(Mcr, ylim = c(-3,3))
plot(Fcr, ylim = c(-3,3))
```

What is the absolute scale for these effects?

10. Compare the fit of the naive model with just age and the three-factor models, using `anova`, e.g.:

```
anova(Mcr, r.m, test = "Chisq")
```

What do you conclude?

11. The model we fitted has three time-scales: current age, current date and current duration of diabetes, so the effects that we report are not immediately interpretable, as they are (as in any kind of multiple regressions) to be interpreted as “all else equal” which they are not, as the three time scales advance simultaneously at the same pace. The reporting would therefore more naturally be on the mortality scale as a function of age, but showing the mortality for persons diagnosed in different ages, using separate displays for separate years of diagnosis. This is most easily done using the `ci.pred` function with the `newdata =` argument. So a person diagnosed in age 50 in 1995 will have a mortality measured in cases per 1000 PY as:

```
pts <- seq(0, 12, 1/4)
nd <- data.frame(A = 50 + pts,
  P = 1995 + pts,
  dur = pts)
m.pr <- ci.pred(Mcr, newdata = nd)
```

Note that because we used `gam.Lexis` which uses the `thepoisreg` family we need not specify `lex.dur` as a variable in the prediction data frame `nd`. Predictions will be rates in the same units as `lex.dur`. Now take a look at the result from the `ci.pred` statement and construct prediction of mortality for men and women diagnosed in a range of ages, say 50, 60, 70, and plot these together in the same graph:

```
cbind(nd, ci.pred(Mcr, newdata = nd))
```

12. From figure it seems that the duration effect is over-modeled, so refit constraining the d.f. to 5:

```
Mcr <- gam.Lexis(subset(SL, sex == "M"),
  ~ s( A, bs = "cr", k = 10) +
    s( P, bs = "cr", k = 10) +
    s(dur, bs = "cr", k = 5))
summary(Mcr)
Fcr <- gam.Lexis(subset(SL, sex == "F"),
  ~ s( A, bs = "cr", k = 10) +
    s( P, bs = "cr", k = 10) +
    s(dur, bs = "cr", k = 5))
```

How does `gam.check()` look for these models? Plot the estimated rates from the revised models. What do you conclude from the plots?

SMR

The SMR is the **S**tandardized **M**ortality **R**atio, which is the mortality rate-ratio between the diabetes patients and the general population. In real studies we would subtract the deaths and the person-years among the diabetes patients from those of the general population, but since we do not have access to these, we make the comparison to the general population at large, *i.e.* also including the diabetes patients. So we now want to include the population mortality rates as a fixed variable in the split dataset; for each record in the split dataset we attach the value of the population mortality for the relevant sex, and and calendar time. This can be achieved in two ways: Either we just use the current split of follow-up time and allocate the population mortality rates for some suitably chosen (mid-)point of the follow-up in each, or we make a second split by date, so that follow-up in the diabetes patients is in the same classification of age and data as the population mortality table.

13. We will use the former approach, using the dataset split in 6 month intervals, and then include as an extra variable the population mortality as available from the data set `M.dk`. First create the variables in the diabetes dataset that we need for matching with the population mortality data, that is sex and age and date at the midpoint of each of the intervals (or rather at a point 3 months after the left endpoint of the interval — recall we split the follow-up in 6 month intervals). We need to have variables of the same type when we merge, so we must transform the sex variable in `M.dk` to a factor, and must for each follow-up interval in the `SL` data have an age and a period variable that can be used in merging with the population data.

```
str(SL)
SL$Am <- floor(SL$A + 0.25)
SL$Pm <- floor(SL$P + 0.25)
data(M.dk)
str(M.dk)
M.dk <- transform(M.dk, Am = A,
  Pm = P,
  sex = factor(sex, labels = c("M", "F")))
str(M.dk)
```

Then match the rates from `M.dk` into `SL` — `sex`, `Am` and `Pm` are the common variables, and therefore the match is on these variables:


```
SLr <- merge(SL, M.dk[,c("sex", "Am", "Pm", "rate")])
dim(SL)
dim(SLr)
```

This merge (remember to `?merge!`) only takes rows that have information from both datasets, hence the slightly fewer rows in `SLr` than in `SL`.

14. Compute the expected number of deaths as the person-time multiplied by the corresponding population rate, and put it in a new variable, `E`, say (`Expected`). Use `stat.table` to make a table of observed, expected and the ratio (SMR) by age (suitably grouped, look for `cut`) and sex.
15. Fit a poisson model with sex as the explanatory variable and log-expected as offset to derive the SMR (and c.i.). Some of the population mortality rates are 0, so you need to exclude those records from the analysis.

```
msmr <- glm((lex.Xst == "Dead") ~ sex - 1 + offset(log(E)),
            family = poisson,
            data = subset(SLr, E > 0))
ci.exp(msmr)
```

Recognize the numbers?

16. The same model can be fitted a bit simpler by the `poisreg` family, try:

```
msmr <- glm(cbind(lex.Xst == "Dead", E) ~ sex - 1,
            family = poisreg,
            data = subset(SLr, E > 0))
ci.exp(msmr)
```

We can assess the ratios of SMRs between men and women by using the `ctr.mat` argument which should be a matrix:

```
(CM <- rbind(M = c(1,0),
            W = c(0,1),
            'M/F' = c(1,-1)))
round(ci.exp(msmr, ctr.mat = CM), 2)
```

What do you conclude?

1.13.1 SMR modeling

17. Now model the SMR using age and date of diagnosis and diabetes duration as explanatory variables, including the expected-number instead of the person-years, using separate models for men and women. You cannot use `gam.Lexis` from the code you used for fitting models for the rates, you need to use `gam` with the `poisreg` family. And remember to exclude those units where no deaths in the population occur (that is where the rate is 0). Plot the estimated smooth effects for both men and women using e.g. `plot.gam`. What do you see?
18. Plot the predicted SMRs from the models for men and women diagnosed in ages 50, 60 and 70 as you did for the rates. What do you see?

19. Try to simplify the model to one with a simple sex effect, separate linear effects of age and date of follow-up for each sex, and a smooth effect of duration common for both sexes, giving an estimate of the change in SMR by age and calendar time. How much does SMR change by each year of age? And by each calendar year?
20. Use your previous code to plot the predicted mortality from this model too. Are the predicted SMR curves credible?

1.14 Causal inference

1.14.1 Proper adjustment for confounding in regression models

The first exercise of this session will ask you to simulate some data according to pre-specified causal structure (don't take the particular example too seriously) and see how you should adjust the analysis to obtain correct estimates of the causal effects.

Suppose one is interested in the effect of beer-drinking on body weight. Let's *assume* that in addition to the potential effect of beer on weight, the following is true in reality:

- Men drink more beer than women
- Men have higher body weight than women
- People with higher body weight tend to have higher blood pressure
- Beer-drinking increases blood pressure

The task is to simulate a dataset in accordance with this model, and subsequently analyse it to see, whether the results would allow us to conclude the true association structure.

1. Sketch a causal graph (not necessarily with R) to see, how should one generate the data
2. Suppose the actual effect sizes are following:

- The probability of beer-drinking is 0.2 for females and 0.7 for males
- Men weigh on average 10kg more than women
- One kg difference in body weight corresponds in average to 0.5mmHg difference in (systolic) blood pressures
- Beer-drinking increases blood pressure by 10mmHg in average.
- Beer-drinking has **no** effect on body weight

The R commands to generate the data are:

```
> bdat= data.frame(sex = c(rep(0,500),rep(1,500)) )
> # a data frame with 500 females, 500 males
> bdat$beer <- rbinom(1000,1,0.2+0.5*bdat$sex)
> bdat$weight <- 60 + 10*bdat$sex + rnorm(1000,0,7)
> bdat$bp <- 110 + 0.5*bdat$weight + 10*bdat$beer + rnorm(1000,0,10)
```

3. Now fit the following models for body weight as dependent variable and beer-drinking as independent variable. Look, what is the estimated effect size:
 - (a) Unadjusted (just simple linear regression)
 - (b) Adjusted for sex
 - (c) Adjusted for sex and blood pressure
4. What would be the conclusions on the effect of beer on weight, based on the three models? Do they agree? Which (if any) of the models gives an unbiased estimate of the actual causal effect of interest?

5. How can the answer be seen from the graph?
6. Now change the data-generation algorithm so, that in fact beer-drinking does increase the body weight by 2kg. Look, what are the conclusions in the above models now. Thus the data is generated as before, but the weight variable is computed as:

```
> bdat$weight <- 60 + 10*bdat$sex + 2*bdat$beer + rnorm(1000,0,7)
```

7. Suppose one is interested in the effect of beer-drinking on blood pressure instead, and is fitting a) an unadjusted model for blood pressure, with beer as an only covariate; b) a model with beer, weight and sex as covariates. Would either a) or b) give an unbiased estimate for the effect? (You may double-check whether the simulated data is consistent with your answer).

1.14.2 Instrumental variables estimation, Mendelian randomization and assumptions

In the lecture slides it was shown that in a model for blood glucose level (associated with the risk of diabetes), both BMI and FTO genotype were significant. Seeing such result in a real dataset may misleadingly be interpreted as an evidence of a direct effect of FTO genotype on glucose. Conduct a simulation study to verify that one may see a significant genotype effect on outcome in such model if in fact the assumptions for Instrumental Variables estimation (Mendelian Randomization) are valid – genotype has a direct effect on the exposure only, whereas exposure-outcome association is confounded.

1. Start by generating the genotype variable as $\text{Binomial}(2,p)$, with $p = 0.2$:

```
> n <- 10000
> mrdat <- data.frame(G = rbinom(n,2,0.2))
> table(mrdat$G)
```

2. Also generate the confounder variable U

```
> mrdat$U <- rnorm(n)
```

3. Generate a continuous (normally distributed) exposure variable BMI so that it depends on G and U . Check with linear regression, whether there is enough power to get significant parameter estimates. For instance:

```
> mrdat$BMI <- with(mrdat, 25 + 0.7*G + 2*U + rnorm(n) )
```

4. Finally generate Y ("Blood glucose level") so that it depends on BMI and U (but not on G).

```
> mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + rnorm(n,0,0.5) )
```

5. Verify, that simple regression model for Y , with BMI as a covariate, results in a biased estimate of the causal effect (parameter estimate is different from what was generated) How different is the estimate from 0.1?

6. Estimate a regression model for Y with two covariates, G and BMI . Do you see a significant effect of G ? Could you explain analytically, why one may see a significant parameter estimate for G there?
7. Find an IV (instrumental variables) estimate, using G as an instrument, by following the algorithm in the lecture notes (use two linear models and find a ratio of the parameter estimates). Does the estimate get closer to the generated effect size?

```
> mgx<-lm(BMI ~ G, data=mrdat)
> ci.lin(mgx) # check the instrument effect
> bgx<-mgx$coef[2] # save the 2nd coefficient (coef of G)
> mgy<-lm(Y ~ G, data=mrdat)
> ci.lin(mgy)
> bgy<-mgy$coef[2]
> causeff <- bgy/bgx
> causeff # closer to 0.1?
```

8. A proper simulation study would require the analysis to be run several times, to see the extent of variability in the parameter estimates. A simple way to do it here would be using a `for`-loop. Modify the code as follows (exactly the same commands as executed so far, adding a few lines of code to the beginning and to the end):

```
> n <- 10000
> # initializing simulations:
> # 30 simulations (change it, if you want more):
> nsim<-30
> mr<-rep(NA,nsim) # empty vector for the outcome parameters
> for (i in 1:nsim) { # start the loop
+ ### Exactly the same commands as before:
+ mrdat <- data.frame(G = rbinom(n,2,0.2))
+ mrdat$U <- rnorm(n)
+ mrdat$BMI <- with(mrdat, 25 + 0.7*G + 2*U + rnorm(n) )
+ mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + rnorm(n,0,0.5) )
+ mgx<-lm(BMI ~ G, data=mrdat)
+ bgx<-mgx$coef[2]
+ mgy<-lm(Y ~ G, data=mrdat)
+ bgy<-mgy$coef[2]
+ # Save the i'th parameter estimate:
+ mr[i]<-bgy/bgx
+ } # end the loop
```

Now look at the distribution of the parameter estimate:

```
> summary(mr)
```

9. (*optional*) Change the code of simulations so that the assumptions are violated: add a weak direct effect of the genotype G to the equation that generates Y :

```
> mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + 0.05*G + rnorm(n,0,0.5) )
```

Repeat the simulation study to see, what is the bias in the average estimated causal effect of BMI on Y .

10. (*optional*) Using library `sem` and function `tsls`, obtain a two-stage least squares estimate for the causal effect. Do you get the same estimate as before?

```
> library(sem)
> summary(tsls(Y ~ BMI, ~G, data=mrdat))
```

Why are simulation exercises useful for causal inference?

If we simulate the data, we know the data-generating mechanism and the “true” causal effects. So this is a way to check, whether an analysis approach will lead to estimates that correspond to what is generated. One could expect to see similar phenomena in real data analysis, if the data-generation mechanism is similar to what was used in simulations.

1.15 Causal inference 2: Model-based estimation of causal estimands

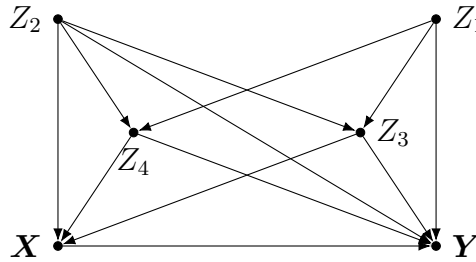
Sources of inspiration: [Luque Fernandez, M.A. et al. \(2018\)](#) *Stat Med* 2018;37(16):2530-2546 and

[Smith et al. \(2022\)](#) *Stat Med* 2022;41(2):407-432.

We shall illustrate with simulated data the estimation of causal effects of a binary exposure X when the outcome Y is also binary, and there is a set of four covariates $Z = (Z_1, Z_2, Z_3, Z_4)$. As a background story, we imagine a population of cancer patients, in whom the variables and the assumed marginal distributions of the covariates are

- X = treatment; 1: radiotherapy only, 0: radiotherapy + chemotherapy,
- Y = death during one year after diagnosis of cancer,
- Z_1 = sex; 0: man, 1: woman; $Z_1 \sim \text{Bern}(0.5)$,
- Z_2 = age group 0: “young”, 1: “old”; $Z_2 \sim \text{Bern}(0.65)$,
- Z_3 = stage of cancer; 4 classes; $Z_3 \sim \text{DiscUnif}(1, \dots, 4)$,
- Z_4 = comorbidity score; 5 classes; $Z_4 \sim \text{DiscUnif}(1, \dots, 5)$.

For simplicity, covariates Z_3 and Z_4 are treated as continuous variables in the models. The assumed causal diagram is shown below.



For more generic notation, the probabilities of $Y = 1$ will be expressed as expectations, e.g. $E(Y^{X=x}) = P(Y^{X=x} = 1)$ and $E(Y|X = x, Z = z) = P(Y = 1|X = x, Z = z)$, where Z is the vector of relevant covariates. The same principle is applied in expressing the conditional probability of $X = 1$ given $Z = z$. The fitted or predicted probabilities of $Y = 1$ are denoted as fitted \hat{Y} or predicted values \tilde{Y} of Y with pertinent subscripts and/or superscripts. Both X and Y are modelled by logistic regression. The expit-function or inverse of the logit function is defined: $\text{expit}(u) = 1/(1 + e^{-u})$, $u \in \mathbb{R}$. This is equal to the cumulative distribution function of the standard logistic distribution, the values of which are returned in R by `plogis(u)`. The R function that returns values of the logit-function is `qlogis()`.

The true model assumed for the dependence of exposure X on covariates:

$$E(X|Z_1 = z_1, \dots, Z_4 = z_4) = \text{expit}(-5 + 0.05z_2 + 0.25z_3 + 0.5z_4 + 0.4z_2z_4).$$

The assumed true model for the outcome is

$$E(Y|X = x, Z_1 = z_1, \dots, Z_4 = z_4) = \text{expit}(-1 + x - 0.1z_1 + 0.35z_2 + 0.25z_3 + 0.20z_4 + 0.15z_2z_4)$$

Note that X does not depend on Z_1 , and that in both models there is a product term Z_2Z_4 , which appears weaker for the outcome model.

1.15.1 Control of confounding

1. Based on inspection of the causal diagram, can you identify a proper subset from the four covariates, which would be sufficient to block all backdoor paths between X and Y and thus remove confounding?
2. Even if such a minimal sufficient set is found in item (a), why could it still be worth while to include all covariates when modelling the outcome?

1.15.2 Generation of target population and true models

1. Load the necessary packages.

```
> library(Epi)
> library(stdReg)
> library(PWeight)
> library(SuperLearner)
> library(tmle)
```

2. Define the R-functions for the true outcome model and the true exposure model.

```
> EX <- function( z2, z3, z4 ) {
+   plogis(-5 + 0.05*z2 + 0.25*z3 + 0.5*z4 + 0.4*z2*z4) }
> EY <- function(x, z1, z2, z3, z4) {
+   plogis(-1 + x - 0.1*z1 + 0.35*z2 + 0.25*z3 +
+     0.20*z4 + 0.15*z2*z4) }
```

3. Define the function for the generation of data based on the given assumptions

```
> genData <- function(N) {
+   z1 <- rbinom(N, size=1, prob=0.5)           # Bern(0.5)
+   z2 <- rbinom(N, size=1, prob=0.65)          # Bern(0.65)
+   z3 <- trunc(runif(N, min=1, max=5), digits=0) # DiscUnif(1,4)
+   z4 <- trunc(runif(N, min=1, max=6), digits=0) # DiscUnif(1,5)
+   x <- rbinom(N, size=1, prob=EX(z2, z3, z4) )
+   y <- rbinom(N, size=1, prob=EY(x, z1, z2, z3, z4) )
+   data.frame(z1, z2, z3, z4, x, y)
+ }
```

4. Generate a data frame `dd` for a big target population of 500000 subjects

```
> N <- 500000
> set.seed(7777)
> dd <- genData(N)
```


1.15.3 Factual and counterfactual risks – associational and causal contrasts

1. Compute the factual risks of death for the two exposure groups

$$E(Y|X = x) = P(Y = 1|X = x) = \frac{P(Y = 1 \& X = x)}{P(X = x)}, \quad x = 0, 1,$$

in the whole target population, as well as their associational contrasts: risk difference, risk ratio, and odds ratio. Before that define a useful function

```
> Contr <- function(mu1, mu0) {
+   RD <- mu1 - mu0
+   RR <- mu1/mu0
+   OR <- (mu1/(1-mu1)) / (mu0/(1-mu0))
+   return(c(mu1, mu0, RD=RD, RR=RR, OR=OR))
+ }
> Ey1 <- with(dd, sum(y==1 & x==1)/sum(x==1) )
> Ey0 <- with(dd, sum(y==1 & x==0)/sum(x==0) )
> round(Contr(Ey1, Ey0), 4)
```

How much bigger is the risk of death of those exposed to radiotherapy only as compared with those receiving chemotherapy, too?

2. Compute the counterfactual risks of death $E(Y_i^{X_i=x}) = P(Y_i^{X_i=x} = 1) = \pi_i^{X_i=x}$ for each individual under the alternative treatments or exposure values $x = 0, 1$ with given covariate values, the average or overall counterfactual risks $E(Y^{X=1}) = \pi^1$ and $E(Y^{X=0}) = \pi^0$ in the population, and the true marginal causal contrasts for the effect of X :

$$\begin{aligned} \text{RD} &= E(Y^{X=1}) - E(Y^{X=0}), & \text{RR} &= E(Y^{X=1})/E(Y^{X=0}), \\ \text{OR} &= \frac{E(Y^{X=1})/[1 - E(Y^{X=1})]}{E(Y^{X=0})/[1 - E(Y^{X=0})]} \end{aligned}$$

```
> dd <- transform(dd, EY1.ind = EY(1, z1, z2, z3, z4),
+   EY0.ind = EY(0, z1, z2, z3, z4) )
> EY1 <- mean(dd$EY1.ind)
> EY0 <- mean(dd$EY0.ind)
> round(Contr(EY1, EY0), 4)
```

3. Compare the associational contrasts in item (a) with the causal contrasts in item (b). What do you conclude about confoundedness of the associational contrasts?

1.15.4 Outcome modelling and estimation of causal contrasts by g-formula

As the first approach for estimating causal contrast of interest we apply the method of standardization or g-formula. Is based on a hopefully realistic enough model for $E(Y|X = x, Z = z)$, i.e. how the probability of outcome is expected to depend on the

exposure variable X and on a sufficient set Z of confounders. The counterfactual risks are marginal expectations of the above quantities, standardized over the joint distribution of the confounders Z in the target population.

$$E(Y^{X=x}) = E_Z[E(Y|X=x, Z)] = \int E(Y|X=x, Z=z) dF_Z(z), \quad x=0, 1.$$

1. Assume now a – slightly misspecified – model mY for the outcome, which contains only main effect terms of the explanatory variables:

$$\pi_i = E(Y_i|X_i = x_i, Z_{i1} = z_{i1}, \dots, Z_{i4} = z_{i4}) = \text{expit} \left(\beta_0 + \delta x_i + \sum_{j=1}^4 \beta_j z_{ij} \right)$$

Fit this model for the whole population in order to have an accurate estimate of the possible bias due to misspecification of the outcome model

```
> mY <- glm(y ~ x + z1 + z2 + z3 + z4, family = binomial, data = dd)
> round(ci.lin(mY, Exp=TRUE)[, c(1,5)], 3)
```

There is not much idea in looking at the standard errors or confidence intervals in such a big target population.

2. For each subject i , compute the fitted individual risk \hat{Y}_i as well as the predicted counterfactual risks $\tilde{Y}_i^{X_i=x}$ for both exposure levels $x=0, 1$ separately, keeping the individual values of the Z -variables as they are.

```
> dd$yh <- predict(mY, type = "response")
> dd$yp1 <- predict(mY, newdata=data.frame( x=rep(1,N),
+      dd[,c("z1","z2","z3","z4")]), type = "response")
> dd$yp0 <- predict(mY, newdata=data.frame( x=rep(0,N),
+      dd[,c("z1","z2","z3","z4")]), type = "response")
```

3. Applying the method of standardization or g-formula compute the point estimates

$$\hat{E}_g(Y^{X=x}) = \frac{1}{n} \sum_{i=1}^n \tilde{Y}_i^{X_i=x}, \quad x=0, 1.$$

of the two counterfactual risks $E(Y^{X=1}) = \pi^1$ and $E(Y^{X=0}) = \pi^0$ as well as the marginal causal contrasts

```
> EY1.g <- mean(dd$yp1)
> EY0.g <- mean(dd$yp0)
> round(Contr(EY1.g, EY0.g), 4)
```

The expectations $E_Z[E(X=x, Z)]$ taken over the joint distribution of the confounders Z are empirically estimated from the data by simply computing the arithmetic means of the individually predicted values $\tilde{Y}_i^{X_i=x}$ of the outcome for the two exposure levels.

Compare the estimated contrast with the true ones in item 3(b) above. How big was the bias due to slight misspecification of the outcome model? Compare in particular the estimate of the marginal OR here with the conditional OR obtained in item (a) from the pertinent coefficient in the logistic model. Which one is closer to 1?

4. Perform the same calculations using the tools in package `stdReg` (see [Sjölander 2016](#))

```
> mY.std <- stdGlm(fit=mY, data=dd, X="x")
> summary(mY.std)
> round(summary(mY.std, contrast = "difference", reference=0)$est.table, 4)
> round(summary(mY.std, contrast = "ratio", reference=0)$est.table, 4)
> round(summary(mY.std, transform="odds",
+               contrast = "ratio", reference=0)$est.table, 4)
```

Check that you got the same point estimates as in the previous item. Again, the confidence intervals are not very meaningful when analysing the data covering the whole big target population. Of course, when applied to sample data they are relevant. In `stdReg` package, the standard errors are obtained by the multivariate delta method built upon M-estimation and robust sandwich estimator of the pertinent covariance matrix, and approximate confidence intervals are derived from these in the usual way.

5. If we are interested in the causal contrasts describing the effect of exposure among those exposed (like ATT), the relevant factual and counterfactual risks in that subset are

$$\pi_1^1 = E(Y^{X=1}|X = 1) = E(Y|X = 1) = \pi_1,$$

$$\pi_1^0 = E(Y^{X=0}|X = 1) = \sum_{X_i=1} E(Y|X = 0, Z = z)P(Z = z|X = 1)$$

We are thus making an “observed vs. expected” comparison, in which the z -specific risks in the unexposed are weighted by the distribution of Z in the exposed subset of the target population. The risks and their contrasts are estimated from the fit of the outcome model:

```
> EY1att.g <- mean(subset(dd, x==1)$yp1)
> EY0att.g <- mean(subset(dd, x==1)$yp0)
> round(Contr(EY1att.g, EY0att.g), 4)
```

Compare the results here with those for the whole target population. What do you observe? Any guess about the causal effect of exposure among the unexposed; is it bigger or smaller than among the exposed or among the whole population?

6. Incidentally, the true causal contrasts among the exposed based on the true model are similarly obtained from the quantities in item 3(b) above:

```
> EY1att <- mean(subset(dd, x==1)$EY1.ind)
> EY0att <- mean(subset(dd, x==1)$EY0.ind)
> round(Contr(EY1att, EY0att), 4)
```

Compare the estimates in the previous item with the true values obtained here.

1.15.5 Inverse probability weighting (IPW) by propensity scores, and augmented IPW

The next method is based on weighting each individual observation by the inverse of the probability of belonging to that particular exposure group, which was realized, this probability being predicted by determinants of exposure.

1. Fit first a model for the exposure including main effects of the Z -variables only.

$$p_i = E(X_i | Z_{1i} = z_{1i}, \dots, Z_{4i} = z_{4i}) = \text{expit}(\gamma_0 + \gamma_1 z_{1i} + \gamma_2 z_{2i} + \gamma_3 z_{3i} + \gamma_4 z_{4i}), \quad i = 1, \dots, N$$

```
> mX <- glm(x ~ z1 + z2 + z3 + z4,
+          family = binomial(link=logit), data = dd)
> round(ci.lin(mX, Exp=TRUE)[, c(1, 5)], 4)
```

2. Extract the propensity scores, i.e. fitted probabilities of belonging to exposure group 1: $PS_i = \hat{p}_i$, and compare their distribution between the exposure groups.

```
> dd$PS = predict(mX, type = "response")
> summary(dd$PS)
> with( subset(dd, x==0), plot(density(PS), lty=2) )
> with( subset(dd, x==1), lines(density(PS), lty=1) )
```

How different are the distributions? Are they sufficiently overlapping?

3. Compute the weights $W_i = 1/PS_i$, when $X_i = 1$, and $W_i = 1/(1 - PS_i)$, when $X_i = 0$. Look at the sum as well as the distribution summary of the weights in the exposure groups. The sum of weights should be close to n in both groups.

```
> dd$w <- ifelse(dd$x==1, 1/dd$PS, 1/(1-dd$PS) )
> with(dd, tally(w, x, sum))
```

4. Compute now the weighted estimates of the counterfactual risks for both exposure categories

$$\hat{E}_w(Y^{X=x}) = \frac{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i Y_i}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} = \frac{\sum_{X_i=x} W_i Y_i}{\sum_{X_i=x} W_i}, \quad x = 0, 1,$$

and their causal contrasts, for instance

$$\widehat{RD}_w = \hat{E}_w(Y^{X=1}) - \hat{E}_w(Y^{X=0}) = \frac{\sum_{i=1}^n X_i W_i Y_i}{\sum_{i=1}^n X_i W_i} - \frac{\sum_{i=1}^n (1 - X_i) W_i Y_i}{\sum_{i=1}^n (1 - X_i) W_i}$$

```
> EY1.w <- sum( dd$x * dd$w * dd$y ) / sum( dd$x * dd$w )
> EY0.w <- sum( (1-dd$x) * dd$w * dd$y ) / sum( (1-dd$x) * dd$w )
> round(Contr(EY1.w, EY0.w), 4)
```

The estimate seems to be downward biased. Could this be so, because of ignoring the relatively strong product term effect of Z_2 and Z_4 ?

5. Let us attempt to correct the estimates by a double robust approach called augmented IPW estimation (AIPW), which combines the g-formula and the IPW approach. The AIPW-estimator can be expressed in two ways: either an IPW-corrected g-formula estimator, or a g-corrected IPW-estimator.

$$\begin{aligned} \hat{E}_a(Y^{X=x}) &= \hat{E}_g(Y^{X=x}) + \frac{1}{n} \sum_{i=1}^n \frac{\mathbf{1}_{\{X_i=x\}} W_i (Y_i - \tilde{Y}_i^{X_i=x})}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} \\ &= \hat{E}_w(Y^{X=x}) - \frac{1}{n} \sum_{i=1}^n \left[\frac{\mathbf{1}_{\{X_i=x\}} W_i}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} - 1 \right] \tilde{Y}_i^{X_i=x}. \end{aligned}$$

```
> EY1.a <- EY1.g + mean(dd$x *(dd$y - dd$yp1)*dd$w/sum(dd$x*dd$w) )
> ## or EY1.w - mean( ( ( dd$x*dd$w /sum(dd$x*dd$w) ) - 1 )*dd$yp1 )
> EY0.a <- EY0.g + mean( (1 - dd$x)*(dd$y - dd$yp0)*dd$w/sum((1-dd$x)*dd$w) )
> ## or EY0.w - mean( ( ( (1-dd$x)*dd$w/sum((1-dd$x)*dd$w) ) - 1 )*dd$yp0 )
> round(Contr(EY1.a, EY0.a), 4)
```

Compare these results with those obtained by g-formula and by non-augmented IPW method. Was augmentation successful?

1.15.6 Improving IPW estimation and using R package PSweight

We now try to improve IPW-estimation by a richer exposure model. In computations we shall utilize the R package `PSweight` (see [PSweight vignette](#)).

1. First, we compute the weights from a more flexible exposure model which contains all pairwise product terms of the parents of X . According to the causal diagram, Z_1 is not in that subset, so it is left out. The exposure model is specified and the weights are obtained as follows.

```
> mX2 <- glm(x ~ (z2 + z3 + z4)^2, family=binomial, data=dd)
> round(ci.lin(mX2, Exp=TRUE)[, c(1,5)], 3)
> psw <- SumStat(ps.formula=mX2$formula, data=dd,
+ weight=c("IPW", "treated", "overlap"))
> dd$PS2 <- psw$propensity[, 2] # propensity scores extracted
> plot(density(dd$PS2[dd$x==0]), lty=2 )
> lines(density(dd$PS2[dd$x==1]), lty=1)
```

Note that apart from ordinary IPW, other types of weights can also be obtained. These are relevant when estimating other causal contrasts, like “average treatment effect among the treated” (ATT) and “average treatment effect in the overlap (or equipoise) population” (ATO).

2. `PSweight` includes some useful tools to examine the properties of the distribution and to check the balance of the propensity scores, for instance

```
> plot(psw, type="balance", metric="PSD")
```

It is desirable that the horizontal values of these measures for given weights are less than 0.1.

3. Estimation and reporting of the causal contrasts. For relative contrasts, the summary method provides the results on the log-scale.

```
> ipwest <- PSweight(ps.formula=mX2, yname="y", data = dd, weight= "IPW")
> ipwest
> summary(ipwest)
> ( logRR.ipw <- summary(ipwest, type="RR") )
> round( exp(logRR.ipw$estimates[c(1,4,5)]), 3)
> round( exp(summary(ipwest, type="OR")$estimates[c(1,4,5)]), 3)
```

Compare these with the previous IPW estimate and the AIPW estimate as well as the true values. Have we obtained nearly unbiased results?

The standard errors provided by `PSweight` are by default based on the empirical sandwich covariance matrix and application of delta method as appropriate.

Bootstrapping is also possible but is computationally very intensive and is recommended to be used only in relatively small samples.

4. If we are interested in the effect of exposure among the exposed (like ATT) then the weights are $W_i = 1$ for the exposed and $W_i = PS_i/(1 - PS_i)$ for the unexposed. Call again `PSweight` but with another choice of weight:

```
> psatt <- PSweight(ps.formula=mX2, yname="y", data = dd, weight= "treated")
> psatt
> round( summary(psatt)$estimates[1], 4)
> round( exp(summary(psatt,type="RR")$estimates[1]), 3)
> round( exp(summary(psatt, type="OR")$estimates[1]), 3)
```

Compare the results here with those obtained by `g-formula` in item 4(e) and with the true contrasts in item 4(f) above.

1.15.7 Targeted maximum likelihood estimation (TMLE)

We now consider now another double robust approach, known as targeted maximum likelihood estimation (TMLE). It also corrects the estimator obtained from the outcome model by elements that are derived from the exposure model.

1. The first step is to utilize the propensity scores obtained above and define the so called clever covariates

```
> dd$H1 <- dd$x / dd$PS2
> dd$H0 <- (1-dd$x) / (1 - dd$PS2)
```

2. Then, a working model is fitted for the outcome, in which the clever covariates are explanatory variables, but the model also includes the previously fitted linear predictor $\hat{\eta}_i = \text{logit}(\hat{Y}_i)$ from the original outcome model `mY` as an offset term.

```
> epsmod <- glm( y ~ -1 + H0 + H1 + offset(qlogis(yh)),
+   family = binomial(link=logit), data=dd )
> eps <- coef(epsmod)
> eps
```

3. The logit-transformed predicted values $\tilde{Y}_i^{X_i=1}$ and $\tilde{Y}_i^{X_i=0}$ of counterfactual individual risks from the original outcome model are now corrected by the estimated coefficients of the clever covariates, and the corrected predictions are returned to the original scale.

```
> yp0.H <- plogis( qlogis(dd$yp0) + eps[1] / (1 - dd$PS2) )
> yp1.H <- plogis( qlogis(dd$yp1) + eps[2] / dd$PS2 )
```

Estimates of the causal contrasts:

4.

```
> EY0.t <- mean(yp0.H)
> EY1.t <- mean(yp1.H)
> round(Contr(EY1.t, EY0.t), 4)
```

Compare these with previous results and with the true values.

1.15.8 TMLE with SuperLearner

Let us finally apply some fashionable tools of statistical learning, aka “machine learning”, using the package **SuperLearner** to fit flexible models for both exposure and outcome. As this method is computationally much more demanding, we illustrate its use by a sample of 2000 subjects only.

1. A simple random sample of $n = 2000$ is drawn from the population.

```
> set.seed(7622)
> n <- 2000
> sampind <- sample(N, n)
> samp <- dd[sampind, ]
```

2. The algorithms to be used in this exercise are chosen

```
> SL.library <- c("SL.glm" , "SL.step", "SL.step.interaction",
+               "SL.glm.interaction", "SL.gam",
+               "SL.randomForest", "SL.rpart")
```

3. Function `tmle()` computes estimates of the causal contrasts of interest. Argument **A** is for the exposure variable, and argument **W** contains the confounders. – The run can take a while ...

```
> tmlest <- tmle(Y = samp$y, A = samp$x, W = samp[,c("z1", "z2", "z3", "z4")],
+               family = "binomial", Q.SL.library = SL.library,
+               g.SL.library = SL.library)
> summary(tmlest)
```

Let us take a closer look at the results. In the beginning are reported the fractions by which the separate algorithms contribute to the combined algorithm. After that are given estimates of the causal contrasts together with their estimated variances and 95 % confidence intervals. The variance of each contrast (on log-scale for RR and OR) is estimated as the variance of the empirical influence curve divided by n , the number of i.i.d. units of observation. Furthermore, causal risk differences are estimated also for those factually exposed and unexposed, respectively.

Note that because this analysis was based on sample data, the estimates are most probably deviating from the true values because of pure random error. Therefore it is not possible to assess the magnitude of a possible bias from a single sample.

4. **Homework.** When you have more time, try to run `tmle` on as large sample as is possible and compare its results with previous ones computed for the whole target population.

1.16 Nested case-control study and case-cohort study: Risk factors of coronary heart disease

In this exercise we shall apply both the nested case-control (NCC) design and the case-cohort (CC) design in sampling control subjects from a defined cohort or closed study population. The case group comprises those cohort members who die from coronary heart disease (CHD) during a > 20 years follow-up of the cohort. The risk factors of interest are cigarette smoking, systolic blood pressure, and total cholesterol level.

Our study population is an occupational cohort comprising 1501 men working in blue-collar jobs in one Nordic country. Eligible subjects had no history of coronary heart disease when recruited to the study in the early 1990s. Smoking habits and many other items were inquired at baseline by a questionnaire, and blood pressure was measured by a research nurse, the values being written down on the questionnaire. Serum samples were also taken from the cohort members at the same time and were stored in a freezer. For some reason, the data in the questionnaires were not entered to any computer file, but the questionnaires were kept in a safe storehouse for further purposes. Also, no biochemical analyses were initially performed for the sera collected from the participants. However, dates of birth and dates of entry to the study were recorded in an electronic file.

In 2010 the study was suddenly reactivated by those investigators of the original team who were still alive then. As the first step mortality follow-up of the cohort members was executed by record linkage to the national population register, from which the dates of death and emigration were obtained. Another linkage was performed with the national register of causes of death in order to get the deaths from coronary heart disease identified. As a result a data file `occoh.txt` was completed containing the following variables:

<code>id</code>	= identification number,
<code>birth</code>	= date of birth,
<code>entry</code>	= date of recruitment and baseline measurements,
<code>exit</code>	= date of exit from mortality follow-up,
<code>death</code>	= indicator for vital status at the end of follow-up, = 1, if dead from any cause, and = 0, if alive,
<code>chdeath</code>	= indicator for death from coronary heart disease, = 1, if “yes”, and 0, if “no”.

This exercise is divided into five main parts:

- (1) Description of the study base or the follow-up experience of the whole cohort, identification of the cases and illustrating the risk sets.
- (2) Nested case-control study within the cohort: (i) selection of controls by risk set or time-matched sampling using function `ccwc()` in package `Epi`, (ii) collection of exposure data for cases and controls from the pertinent data base of the whole cohort to the case-control data set using function `merge()`, and (iii) analysis of the case-control data set with stratified Cox model using function `clogit()` in package `survival()`,
- (3) Case-cohort study within the cohort: (i) selection of a subcohort by simple random sampling from the cohort, (ii) collection of exposure data for subcohort members and cases, and (iii) analysis of the case-cohort data set with Cox model by weighted partial

likelihood including appropriate weighting and correction of estimated covariance matrix for the model coefficients using function `cch()` in package `survival()`.

- (4) Comparison of results from all previous analyses, also with those from a full cohort design.
- (5) Further tasks and homework.

1.16.1 Reading the cohort data, illustrating the study base and risk sets

5. Load the packages `Epi` and `survival`. Read in the cohort data file and name the resulting data frame as `oc`. See its structure and print the univariate summaries.

```
> library(Epi)
> library(survival)
> url <- "https://raw.githubusercontent.com/SPE-R/SPE/master/pracs/data"
> oc <- read.table( paste(url, "occoh.txt", sep = "/"), header=TRUE)
> str(oc)
> summary(oc)
```

6. It is convenient to change all the dates into fractional calendar years

```
> oc$ybirth <- cal.yr(oc$ybirth)
> oc$yentry <- cal.yr(oc$yentry)
> oc$yexit <- cal.yr(oc$yexit)
```

We shall also compute the age at entry and at exit, respectively, as age will be the main time scale in our analyses.

```
> oc$agentry <- oc$yentry - oc$ybirth
> oc$agexit <- oc$yexit - oc$ybirth
```

7. As the next step we shall create a `lexis` object from the data frame along the calendar period and age axes, and as the outcome event we specify the coronary death.

```
> oc.lex <- Lexis( entry = list( per = yentry,
+                               age = yentry - ybirth ),
+                 exit = list( per = yexit),
+                 exit.status = chdeath,
+                 id = id, data = oc)
> str(oc.lex)
> summary(oc.lex)
```

8. At this stage it is informative to examine a graphical presentation of the follow-up lines and outcome cases in a conventional Lexis diagram. Make use of the `plot` method for `Lexis` objects. Gray lifelines are drawn and a bullet is put at the exit point of those lifelines that end with the outcome event.

```
> par(mfrow=c(1,1))
> plot( oc.lex, xlim=c(1990, 2010),grid=TRUE )
> points( oc.lex, pch=c(NA, 16)[oc.lex$lex.Xst+1] )
```

9. As age is here the main time axis, we shall graphically illustrate the **study base**, *i.e.* the follow-up lines and outcome events, only along the age scale, being ordered by age at exit. Vertical lines at those ages when new coronary deaths occur are drawn to identify the pertinent **risk sets**. For that purpose it is useful first to sort the data frame and the **Lexis** object jointly by age at exit & age at entry, and to give a new ID number according to that order.

```
> oc.ord <- cbind(ID = 1:1501, oc[ order( oc$agexit, oc$agentry), ] )
> oc.lexord <- Lexis( entry = list( age = agentry ),
+                   exit = list( age = agexit),
+                   exit.status = chdeath,
+                   id = ID, data = oc.ord)
> plot(oc.lexord, "age")
> points(oc.lexord, pch=ifelse(oc.lexord$lex.Xst==1, 16, NA) )
> with( subset(oc.lexord, lex.Xst==1),
+       abline( v=agexit, lty=3))
```

10. For a closer look, we now zoom the graphical illustration of the risk sets into event times occurring between 50 to 58 years. – Copy the last four lines from the previous item and add arguments **xlim** and **ylim** to the call of **plot()**.

```
> plot(oc.lexord, "age", xlim=c(50, 58), ylim=c(5, 65))
> points(oc.lexord, "age", pch=ifelse(oc.lexord$lex.Xst==1, 16, NA))
> with( subset(oc.lexord, lex.Xst==1),
+       abline( v=agexit, lty=3))
```

1.16.2 Nested case-control study

We shall now employ the strategy of **risk-set sampling** or **time-matched** sampling of controls, *i.e.* we are conducting a **nested case-control study** within the cohort.

11. The risk sets are defined according to the age at diagnosis of the case. Further matching is applied for age at entry by 1-year agebands. For this purpose we first generate a categorical variable **agen2** for age at entry

```
> oc.lex$agen2 <- cut(oc.lex$agentry, br = seq(40, 62, 1) )
```

Matched sampling from risk sets may be carried out using function **ccwc()** found in the **Epi** package. Its main arguments are the times of **entry** and **exit** which specify the time at risk along the main time scale (here age), and the outcome variable to be given in the **fail** argument. The number of controls per case is set to be two, and the additional matching factor is given. – After setting the RNG seed (with your own number), make a call of this function and see the structure of the resulting data frame **cactrl** containing the cases and the chosen individual controls.

```
> set.seed(98623)
> cactrl <-
+   ccwc(entry=agentry, exit=agexit, fail=chdeath,
+       controls = 2, match= agen2,
+       include = list(id, agentry),
+       data=oc.lex, silent=FALSE)
> str(cactrl)
```

Check the meaning of the four first columns of the case-control data frame from the help page of function `ccwc()`.

12. Now we shall start collecting data on the risk factors for the cases and their matched controls, including determination of the total cholesterol levels from the frozen sera! The storehouse of the risk factor measurements for the whole cohort is file `occoh-Xdata.txt`. It contains values of the following variables.

`id` = identification number, the same as in `occoh.txt`,
`smok` = cigarette smoking with categories,
 1: “never”, 2: “former”, 3: “1-14/d”, 4: “15+/d”,
`sbp` = systolic blood pressure (mmHg),
`tchol` = total cholesterol level (mmol/l).

```
> ocX <- read.table( paste(url, "occoh-Xdata.txt", sep = "/"), header=TRUE)
> str(ocX)
```

13. In the next step we collect the values of the risk factors for our cases and controls by merging the case-control data frame and the storehouse file. In this operation we utilize function `merge()` to select columns of two data frames: `cactrl` (all columns) and `ocX` (four columns) and to merge these into a single file (see exercise 1.1, subsection 1.1.8, where `merge()` was introduced). The `id` variable in both files is used as the key to link each individual case or control with his own data on risk factors.

```
> oc.ncc <- merge(cactrl, ocX[, c("id", "smok", "tchol", "sbp")],
+   by = "id")
> str(oc.ncc)
```

14. We shall treat smoking as categorical and total cholesterol and systolic blood pressure as quantitative risk factors, but the values of the latter will be divided by 10 to get more interpretable effect estimates.

Convert the smoking variable into a factor.

```
> oc.ncc$smok <- factor(oc.ncc$smok,
+   labels = c("never", "ex", "1-14/d", ">14/d"))
```

15. It is useful to start the analysis of case-control data by simple tabulations by the categorized risk factors. Crude estimates of the rate ratios associated with them, in which matching is ignored, can be obtained as follows. We shall focus on smoking

```
> stat.table( index = list( smok, Fail ),
+   contents = list( count(), percent(smok) ),
+   margins = T, data = oc.ncc )
> smok.crncc <- glm( Fail ~ smok, family=binomial, data = oc.ncc)
> round(ci.exp(smok.crncc), 3)
```

16. A proper analysis takes into account matching that was employed in the selection of controls for each case from the pertinent risk set, further restricted to subjects who were about the same age at entry as the case was. Also, adjustment for the other risk factors is desirable. In this analysis function `clogit()` in `survival` package is utilized. It is in fact a wrapper of function `coxph()`.

```
> m.clogit <- clogit( Fail ~ smok + I(sbp/10) + tchol +
+   strata(Set), data = oc.ncc )
> summary(m.clogit)
> round(ci.exp(m.clogit), 3)
```

Compare these with the crude estimates obtained above.

1.16.3 Case-cohort study

Now we start applying the second major outcome-selective sampling strategy for collecting exposure data from a big study population

17. The subcohort is selected as a simple random sample ($n = 260$) from the whole cohort. The id-numbers of the individuals that are selected will be stored in vector `subcids`, and `subcind` is an indicator for inclusion to the subcohort.

```
> N <- 1501; n <- 260
> set.seed(15792)
> subcids <- sample(N, n )
> oc.lexord$subcind <- 1*(oc.lexord$id %in% subcids)
```

18. We form the data frame `oc.cc` to be used in the subsequent analysis selecting the union of the subcohort members and the case group from the data frame of the full cohort. After that we collect the data of the risk factors from the data storehouse for the subjects in the case-cohort data

```
> oc.cc <- subset( oc.lexord, subcind==1 | chdeath ==1)
> oc.cc <- merge( oc.cc, ocX[, c("id", "smok", "tchol", "sbp")],
+   by = "id")
> str(oc.cc)
```

19. We shall now create a graphical illustration of the lifelines contained in the case-cohort data. Lines for the subcohort non-cases are grey without bullet at exit, those for subcohort cases are blue with blue bullet at exit, and for cases outside the subcohort the lines are red and dotted with red bullets at exit.

```
> plot( subset(oc.cc, chdeath==0), "age")
> lines( subset(oc.cc, chdeath==1 & subcind==1), col="blue")
> lines( subset(oc.cc, chdeath==1 & subcind==0), col="red")
> points(subset(oc.cc, chdeath==1), pch=16,
+   col=c("blue", "red")[oc.cc$subcind+1])
```

20. Define the categorical smoking variable again.

```
> oc.cc$smok <- factor(oc.cc$smok,
+   labels = c("never", "ex", "1-14/d", ">14/d"))
```

A crude estimate of the hazard ratio for the various smoking categories k vs. non-smokers ($k = 1$) can be obtained by tabulating cases (D_k) and person-years (y_k) in the subcohort by smoking and then computing the relevant exposure odds ratio for each category:

$$\text{HR}_k^{\text{crude}} = \frac{D_k/D_1}{y_k/y_1}$$

```
> sm.cc <- stat.table( index = smok,
+   contents = list( Cases = sum(lex.Xst), Pyrs = sum(lex.dur) ),
+   margins = T, data = oc.cc)
> print(sm.cc, digits = c(sum=0, ratio=1))
> HRcc <- (sm.cc[ 1, -5]/sm.cc[ 1, 1])/(sm.cc[ 2, -5]/sm.cc[2, 1])
> round(HRcc, 3)
```

Do these estimates resemble those obtained from nested case-control data?

21. To estimate the rate ratios associated with smoking and adjusted for the other risk factors we now fit the pertinent Cox model applying the method of *weighted partial likelihood* as presented by Ling & Ying (1993) and Barlow (1994). This analysis can be done using function `cch()` in package `survival` with `method = "LinYing"`

```
> oc.cc$survobj <- with(oc.cc, Surv(agentry, agexit, chdeath) )
> cch.LY <- cch( survobj ~ smok + I(sbp/10) + tchol, stratum=NULL,
+   subcoh = ~subcind, id = ~id, cohort.size = N, data = oc.cc,
+   method = "LinYing" )
> summary(cch.LY)
```

1.16.4 Full cohort analysis and comparisons

Finally, suppose the investigators after all could afford to collect the data on risk factors from the storehouse for the whole cohort.

22. Let us form the data frame corresponding to the full cohort design and convert again smoking to be categorical.

```
> oc.full <- merge( oc.lex, ocX[, c("id", "smok", "tchol", "sbp")],
+   by.x = "id", by.y = "id")
> oc.full$smok <- factor(oc.full$smok,
+   labels = c("never", "ex", "1-14/d", ">14/d"))
```

Just for comparison with the corresponding analysis in case-cohort data perform a similar crude estimation of hazard ratios associated with smoking.

```
> sm.coh <- stat.table( index = smok,
+   contents = list( Cases = sum(lex.Xst), Pyrs = sum(lex.dur) ),
+   margins = T, data = oc.full)
> print(sm.coh, digits = c(sum=0, ratio=1))
> HRcoh <- (sm.coh[ 1, -5]/sm.coh[ 1, 1])/(sm.coh[ 2, -5]/sm.coh[2, 1])
> round(HRcoh, 3)
```

23. Fit now the ordinary Cox model to the full cohort. There is no need to employ extra tricks upon the ordinary `coxph()` fit.

```
> cox.coh <- coxph( Surv(agency, ageexit, chdeath) ~
+               smok + I(sbp/10) + tchol, data = oc.full)
> summary(cox.coh)
```

24. Lastly, a comparison of the point estimates and standard errors between the different designs, including variants of analysis for the case-cohort design, can be performed.

```
> betas <- cbind( coef(cox.coh), coef(m.clogit), coef(cch.LY) )
> colnames(betas) <- c("coh", "ncc", "cch.LY")
> round(betas, 3)
> SEs <- cbind( sqrt( diag( cox.coh$var ) ),
+             sqrt( diag( m.clogit$var ) ),
+             sqrt( diag( cch.LY$var ) ) )
> colnames(SEs) <- colnames(betas)
> round(SEs, 3)
```

You will notice that the point estimates of the coefficients obtained from the full cohort, nested case-control, and case-cohort analyses, respectively, are somewhat variable.

However, the standard errors from the NCC and CC analyses should be quite similar when the numbers of cases and non-cases are similar.

1.16.5 Further exercises and homework

25. If you have time, you could run both the NCC study and CC study again but now with a larger control group or subcohort; for example 4 controls per case in NCC and $n = 520$ as the subcohort size in CC. Remember resetting the seed first. Pay attention in the results to how much closer will be the point estimates and the proper SEs to those obtained from the full cohort design.
26. Instead of simple linear terms for `sbp` and `tchol` you could try to fit spline models to describe their effects.
27. A popular alternative to weighted partial likelihood in the analysis of case-cohort data is the *pseudo-likelihood method* (Prentice 1986), which is based on “late entry” to follow-up of the case subjects not belonging to the subcohort. The way to do this is provided by function `cch()` which you can apply directly to the case-cohort data `oc.cc` as before but now with `method = "Prentice"`. – Try this and compare the results with those obtained by weighted partial likelihood in model `cch.LY`.
28. Yet another computational solution for maximizing weighted partial likelihood is provided by a combination of functions `twophase()` and `svycoxph()` of the `survey` package. The approach is illustrated with an example in a vignette “Two-phase designs in epidemiology” by Thomas Lumley (see <http://cran.r-project.org/web/packages/survey/vignettes/epi.pdf>). – You can try this at home and check that you would obtain similar results as with model `cch.LY`.

1.17 Time-dependent variables and multiple states

The following practical exercise is based on the data from paper:

P Hovind, L Tarnow, P Rossing, B Carstensen, and HH Parving: Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. *Kidney Int*, **66**(3):1180–1186, Sept 2004.

You can find a .pdf-version of the paper here:

<http://BendixCarstensen.com/~bxc/AdvCoh/papers/Hovind.2004.pdf>

1.17.1 The renal failure dataset

The dataset `renal.dta` contains data on follow up of 125 patients from Steno Diabetes Center. They enter the study when they are diagnosed with nephrotic range albuminuria (NRA). This is a condition where the levels of albumin in the urine is exceeds a certain level as a sign of kidney disease. The levels may however drop as a consequence of treatment, this is called remission. Patients exit the study at death or kidney failure (dialysis or transplant).

Table 1.2: *Variables in renal.dta.*

<code>id</code>	Patient id
<code>sex</code>	1=male, 2=female
<code>dob</code>	Date of birth
<code>doe</code>	Date of entry into the study (2.5 years after NRA)
<code>dor</code>	Date of remission. Missing if no remission has occurred
<code>dox</code>	Date of exit from study
<code>event</code>	Exit status: 1,2,3=event (death, ESRD), 0=censored

1. The dataset is in Stata-format, so you must read the dataset using `read.dta` from the `foreign` package (which is part of the standard R-distribution). At the same time, convert `sex` to a proper factor. Choose where to read the dataset.

```
library( Epi ) ; clear()
library( foreign )
renal <- read.dta(
  "https://raw.githubusercontent.com/SPE-R/SPE/master/pracs/data/renal.dta")
# renal <- read.dta( "http://BendixCarstensen.com/SPE/data/renal.dta" )
# renal <- read.dta( "./data/renal.dta" )
renal$sex <- factor( renal$sex, labels=c("M","F") )
head( renal )
```

2. Use the `Lexis` function to declare the data as survival data with age, calendar time and time since entry into the study as timescales. Label any event > 0 as “ESRD”, i.e. renal death (death of kidney (transplant or dialysis), or person). Note that you must make sure that the “alive” state (here NRA) is the first, as `Lexis` assumes that everyone starts in this state (unless of course `entry.status` is specified):

```

Lr <- Lexis( entry = list( per=doe,
                           age=doe-dob,
                           tfi=0 ),
             exit = list( per=dor ),
             exit.status = factor( event>0, labels=c("NRA","ESRD") ),
             data = renal )
str( Lr )
summary( Lr )

```

Make sure you know what the variables in `Lr` stand for.

3. Visualize the follow-up in a Lexis-diagram, by using the `plot` method for `Lexis` objects.

```

plot( Lr, col="black", lwd=3 )
subset( Lr, age<0 )

```

What is wrong here? List the data for the person with negative entry age.

4. Correct the data and make a new plot, for example by:

```

Lr <- transform( Lr, dob = ifelse( dob>2000, dob-100, dob ),
                 age = ifelse( dob>2000, age+100, age ) )
subset( Lr, id==586 )
plot( Lr, col="black", lwd=3 )

```

5. (*Optional, esoteric*) We can produce a slightly more fancy Lexis diagram. Note that we have a x -axis of 40 years, and a y -axis of 80 years, so when specifying the output file adjust the *total* width of the plot so that the use of `mai` (look up the help page for `par`) to specify the margins of the plot so that it leaves a plotting area twice as high as wide. The `mai` argument to `par` gives the margins in inches, so the total size of the horizontal and vertical margins is 1 inch each, to which we add $80/5$ in the height, and $40/5$ in the horizontal direction, each giving exactly 5 years per inch in physical size.
6. Now make a Cox-regression analysis of the endpoint ESRD with the variables `sex` and `age` at entry into the study, using time since entry to the study as time scale.

```

library( survival )
mc <- coxph( Surv( lex.dur, lex.Xst=="ESRD" ) ~
             I(age/10) + sex, data=Lr )
summary( mc )

```

What is the The hazard ratio between males and females? Between two persons who differ 10 years in age at entry?

7. The main focus of the paper was to assess whether the occurrence of remission (return to a lower level of albumin excretion, an indication of kidney recovery) influences mortality. "Remission" is a time-dependent variable which is initially 0, but takes the value 1 when remission occurs. In order to handle this, each person who sees a remission must have two records:
 - One record for the time before remission, where entry is `doe`, exit is `dor`, remission is 0, and event is 0.

- One record for the time after remission, where entry is `dor`, exit is `dox`, remission is 1, and event is 0 or 1 according to whether the person had an event at `dox`.

This is accomplished using the `cutLexis` function on the `Lexis` object, where we introduce a remission state “Rem”. You must declare the “NRA” state as a precursor state, i.e. a state that is *less* severe than “Rem” in the sense that a person who see a remission will stay in the “Rem” state unless he goes to the “ESRD” state. Also use `split.state=TRUE` to have different ESRD states according to whether a person had had remission or not prior to ESRD. The statement to do this is:

```
Lc <- cutLexis( Lr, cut = Lr$dor, # where to cut follow up
               timescale = "per", # what timescale are we referring to
               new.state = "Rem", # name of the new state
               split.state = TRUE, # different states depending on previous
               precursor.states = "NRA" ) # which states are less severe
summary( Lc )
```

List the records from a few select persons (choose values for `lex.id`, using for example `subset(Lc, lex.id %in% c(5,7,9))`, or other numbers).

8. Now show how the states are connected and the number of transitions between them by using `boxes`. This is an interactive command that requires you to click in the graph window:

```
boxes( Lc )
```

It has a couple of fancy arguments, try:

```
boxes( Lc, boxpos=TRUE, scale.R=100, show.BE=TRUE, hm=1.5, wm=1.5 )
```

You may even be tempted to read the help page for `boxes.Lexis` ...

9. Plot a Lexis diagram where different coloring is used for different segments of the follow-up. The `plot.Lexis` function draws a line for each record in the dataset, so you can index the coloring by `lex.Cst` and `lex.Xst` as appropriate — indexing by a factor corresponds to indexing by the *index number* of the factor levels, so you must be know which order the factor levels are in:

```
par( mai=c(3,3,1,1)/4, mgp=c(3,1,0)/1.6 )
plot( Lc, col=c("red","limegreen")[Lc$lex.Cst],
      xlab="Calendar time", ylab="Age",
      lwd=3, grid=0:20*5, xlim=c(1970,2010), ylim=c(0,80), xaxs="i", yaxs="i", las=1 )
points( Lc, pch=c(NA,NA,16)[Lc$lex.Xst],
        col=c("red","limegreen","transparent")[Lc$lex.Cst] )
points( Lc, pch=c(NA,NA,1)[Lc$lex.Xst],
        col="black", lwd=2 )
```

10. Make Cox-regression of mortality (i.e. endpoint “ESRD” or “ESRD(Rem)”) with sex, age at entry and remission as explanatory variables, using time since entry as timescale, and include `lex.Cst` as time-dependent variable, and indicate that each record represents follow-up from `tfi` to `tfi+lex.dur`. Make sure that you know why what goes where here in the call to `coxph`.

```

( EP <- levels(Lc)[3:4] )
m1 <- coxph( Surv( tfi,                      # from
                  tfi+lex.dur,              # to
                  lex.Xst %in% EP ) ~      # event
                  sex + I((doe-dob-50)/10) + # fixed covariates
                  (lex.Cst=="Rem"),         # time-dependent variable
                  data = Lc )
summary( m1 )

```

What is the effect of of remission on the rate of ESRD?

1.17.2 Splitting the follow-up time

In order to explore the effect of remission on the rate of ESRD, we shall split the data further into small pieces of follow-up. To this end we use the function `splitLexis`. The rates can then be modeled using a Poisson-model, and the shape of the underlying *rates* be explored. Furthermore, we can allow effects of both time since NRA and current age. To this end we will use splines, so we need the `splines` and also the `mgcv` packages.

11. Now split the follow-up time every month after entry, and verify that the number of events and risk time is the same as before and after the split:

```

sLc <- splitLexis( Lc, "tfi", breaks=seq(0,30,1/12) )
summary( Lc, scale=100 )
summary(sLc, scale=100 )

```

12. Try to fit the Poisson-model corresponding to the Cox-model we fitted previously. The function `Ns()` produces a model matrix corresponding to a piece-wise cubic function, modeling the baseline hazard explicitly (think of the `ns` terms as the baseline hazard that is not visible in the Cox-model). Use teh wrapper function `glm.Lexis`

```

mp <- glm.Lexis(sLc, ~ Ns(tfi, knots = c(0,2,5,10)) +
                  sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"))
ci.exp( mp )

```

How does the effects of sex change from the Cox-model?

13. Try instead using the `gam` function from the `mgcv` package. There is convenience wrapper for this for `Lexis` objects as well:

```

library( mgcv )
mx <- gam.Lexis(sLc,
                ~ s(tfi, k=10) + sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"))
ci.exp( mp, subset=c("Cst","doe","sex") )
ci.exp( mx, subset=c("Cst","doe","sex") )

```

We see that there is virtually no difference between the two approaches in terms of the regression parameters.

14. Extract the regression parameters from the models using `ci.exp` and compare with the estimates from the Cox-model:

```
ci.exp( mx, subset=c("sex","dob","Cst"), pval=TRUE )
ci.exp( m1 )
round( ci.exp( mp, subset=c("sex","dob","Cst") ) / ci.exp( m1 ), 2 )
```

How large is the difference in estimated regression parameters?

15. The model has the same assumptions as the Cox-model about proportionality of rates, but there is an additional assumption that the hazard is a smooth function of time since entry. It seems to be a sensible assumption (well, restriction) to put on the rates that they vary smoothly by time. No such restriction is made in the Cox model. The `gam` model optimizes the shape of the smoother by general cross-validation. Try to look at the shape of the estimated effect of `tfi`:

```
plot( mx )
```

Is this a useful plot?

16. However, `plot` does not give you the *absolute* level of the underlying rates because it bypasses the intercept. So try to predict the rates as a function of `tfi` and the covariates, by setting up a prediction data frame. Note that age in the model specification is entered as `doe-dob`, hence the prediction data frame must have these two variables and not the age, but it is only the difference that matters for the prediction:

```
nd <- data.frame(tfi = seq(0,20,0.1),
                 sex = "M",
                 doe = 1990,
                 dob = 1940,
                 lex.Cst = "NRA")
str(nd)
matshade(nd$tfi, cbind(ci.pred(mp, newdata = nd),
                      ci.pred(mx, newdata = nd)) * 100, plot = TRUE,
         type="l", lwd = 3:4, col = c("black", "forestgreen"),
         log = "y", xlab = "Time since entry (years)",
         ylab = "ESRD rate (per 100 PY) for 50 year man")
```

Try to overlay with the corresponding prediction from the `glm` model using `Ns`.

1.17.3 Prediction from the multistate model

If we want to make proper statements about the survival and disease probabilities we must know not only how the occurrence of remission influences the rate of death/ESRD, but we must also model the occurrence rate of remission itself.

17. The rates of ESRD were modelled by a Poisson model with effects of age and time since NRA — in the models `mp` and `mx`. But if we want to model whole process we must also model the remission rates transition from “NRA” to “Rem”, but the number of events is rather small so we restrict covariates in this model to only time since NRA and sex. Note that only the records that represent follow-up in the “NRA” state should be used; this is most easily done using the `gam.Lexis` function

```

mr <- gam.Lexis(sLc, ~ s( tfi, k=10 ) + sex,
               from = "NRA",
               to = "Rem")
ci.exp(mr, pval = TRUE)

```

What is the remission rate-ratio between men and women?

18. If we want to predict the probability of being in each of the three states using these estimated rates, we may resort to analytical calculations of the probabilities from the estimated rates, which is actually doable in this case, but which will be largely intractable for more complicated models. Alternatively we can *simulate* the life course for a large group of (identical) individuals through a model using the estimated rates. That will give a simulated cohort (in the form of a **Lexis** object), and we can then just count the number of persons in each state at each of a set of time points. This is accomplished using the function `simLexis`. The input to this is the initial status of the persons whose life-course we shall simulate, and the transition rates in suitable form:

- Suppose we want predictions for men aged 50 at NRA. The input is in the form of a **Lexis** object (where `lex.dur` and `lex.Xst` will be ignored). Note that in order to carry over the `time.scales` and the `time.since` attributes, we construct the input object using `subset` to select columns, and `NULL` to select rows (see the example in the help file for `simLexis`):

```

inL <- subset( sLc, select=1:11 )[NULL,]
str( inL )
timeScales(inL)
inL[1,"lex.id"] <- 1
inL[1,"per"] <- 2000
inL[1,"age"] <- 50
inL[1,"tfi"] <- 0
inL[1,"lex.Cst"] <- "NRA"
inL[1,"lex.Xst"] <- NA
inL[1,"lex.dur"] <- NA
inL[1,"sex"] <- "M"
inL[1,"doe"] <- 2000
inL[1,"dob"] <- 1950
inL <- rbind( inL, inL )
inL[2,"sex"] <- "F"
inL
str( inL )

```

- The other input for the simulation is the transitions, which is a list with an element for each transient state (that is “NRA” and “Rem”), each of which is again a list with names equal to the states that can be reached from the transient state. The content of the list will be `glm` objects, in this case the models we just fitted, describing the transition rates:

```

Tr <- list( "NRA" = list( "Rem" = mr,
                        "ESRD" = mx ),
           "Rem" = list( "ESRD(Rem)" = mx ) )

```

With this as input we can now generate a cohort, using `N=5` to simulate life course of 10 persons (5 for each set of starting values in `inL`):

```
( iL <- simLexis( Tr, inL, N=10 ) )
summary( iL, by="sex" )
```

What type of object have you got as `iL`. Simulate a couple of thousand persons.

19. Now generate the life course of 5,000 persons, and look at the summary. The `system.time` command is just to tell you how long it took, you may want to start with 1000 just to see how long that takes.

```
system.time(
  sM <- simLexis( Tr, inL, N = 5000, t.range = 12 ) )
summary( sM, by="sex" )
```

Why are there so many ESRD-events in the resulting data set?

20. Now count how many persons are present in each state at each time for the first 10 years after entry (which is at age 50). This can be done by using `nState`. Try:

```
nStm <- nState( subset(sM,sex=="M"), at=seq(0,10,0.1), from=50, time.scale="age" )
nStf <- nState( subset(sM,sex=="F"), at=seq(0,10,0.1), from=50, time.scale="age" )
head( nStf )
```

What is the object `nStf`?

21. With the counts of persons in each state at the designated time points (in `nStm`), compute the cumulative fraction over the states, arranged in order given by `perm`:

```
ppm <- pState( nStm, perm=c(2,1,3,4) )
ppf <- pState( nStf, perm=c(2,1,3,4) )
head( ppf )
tail( ppf )
```

What do the entries in `ppf` represent?

22. Try to plot the cumulative probabilities using the `plot` method for `pState` objects:

```
plot( ppf )
```

Is this useful?

23. Now try to improve the plot so that it is easier to read, and easier to compare men and women:

```
par( mfrow=c(1,2) )
plot( ppm, col=c("limegreen","red","#991111","forestgreen") )
lines( as.numeric(rownames(ppm)), ppm[, "Rem"], lwd=4 )
text( 59.5, 0.95, "Men", adj=1, col="white", font=2, cex=1.2 )
axis( side=4, at=0:10/10 )
axis( side=4, at=1:99/100, labels=NA, tck=-0.01 )
plot( ppf, col=c("limegreen","red","#991111","forestgreen"), xlim=c(60,50) )
lines( as.numeric(rownames(ppf)), ppf[, "Rem"], lwd=4 )
text( 59.5, 0.95, "Women", adj=0, col="white", font=2, cex=1.2 )
axis( side=2, at=0:10/10 )
axis( side=2, at=1:99/100, labels=NA, tck=-0.01 )
```

What is the 10-year risk of remission for men and women respectively?

Chapter 2

Solutions

There is a chapter for each of the exercises used at the course. This is either a printout of the R-program that performs the analyses, as well as the graphs produced by the programs, or output from an R-weave solution file with a bit more elaborate text.

The code and the output from these programs are also available from the course homepage in <http://BendixCarstensen/SPE/R>; they are called `xxx-s.R`; just before each chapter you will find a line with the text `xxx-s`, indicating that the name of the script will be `xxx-s.R`.

2.3 Tabulation

2.3.1 Introduction

R and its add-on packages provide several different tabulation functions with different capabilities. The appropriate function to use depends on your goal. There are at least three different uses for tables.

The first use is to create simple summary statistics that will be used for further calculations in R. For example, a two-by-two table created by the `table` function can be passed to `fisher.test`, which will calculate odds ratios and confidence intervals. The appearance of these tables may, however, be quite basic, as their principal goal is to create new objects for future calculations.

A quite different use of tabulation is to make “production quality” tables for publication. You may want to generate reports from for publication in paper form, or on the World Wide Web. The package `xtable` provides this capability, but it is not covered by this course.

An intermediate use of tabulation functions is to create human-readable tables for discussion within your work-group, but not for publication. The `Epi` package provides a function `stat.table` for this purpose, and this practical is designed to introduce this function.

2.3.2 The births data

We shall use the births data which concern 500 mothers who had singleton births in a large London hospital. The outcome of interest is the birth weight of the baby, also dichotomised as normal or low birth weight. These data are available in the `Epi` package:

```
> library(Epi)
> data(births)
> names(births)
[1] "id"      "bweight" "lowbw"   "gestwks" "preterm" "matage"  "hyp"
[8] "sex"

> head(births)
  id bweight lowbw gestwks preterm matage hyp sex
1  1   2974     0   38.52      0     34  0  2
2  2   3270     0    NA      NA     30  0  1
3  3   2620     0   38.15      0     35  0  2
4  4   3751     0   39.80      0     31  0  1
5  5   3200     0   38.89      0     33  1  1
6  6   3673     0   40.97      0     33  0  2
```

The housekeeping file for these data is `births-house.r`, which you can download from a location to be specified in the practical. Assuming that you have copied the housekeeping file into the subdirectory `/data` of your working directory, you should now start the session by running this file with the command:

```
> source("data/births-house.r")
```

Make sure you know what the script file has done using `str(births)`.

2.3.3 One-way tables

The simplest table one-way table is created by

```
> stat.table(index = sex, data = births)
```

```
-----
sex    count()
-----
M       264
F       236
-----
```

This creates a count of individuals, classified by levels of the factor `sex`. Compare this table with the equivalent one produced by the `table` function. Note that `stat.table` has a `data` argument that allows you to use variables in a data frame without specifying the frame.

You can display several summary statistics in the same table by giving a list of expressions to the `contents` argument:

```
> stat.table(index = sex, contents = list(count(), percent(sex)), data=births)
```

```
-----
sex    count() percent(sex)
-----
M       264         52.8
F       236         47.2
-----
```

Only a limited set of expressions are allowed: see the help page for `stat.table` for details.

You can also calculate marginal tables by specifying `margin=TRUE` in your call to `stat.table`. Do this for the above table. Check that the percentages add up to 100 and the total for `count()` is the same as the number of rows of the data frame `births`.

```
> stat.table(index = sex, contents = list(count(), percent(sex)),
+   margin=TRUE, data=births)
```

```
-----
sex    count() percent(sex)
-----
M       264         52.8
F       236         47.2

Total    500        100.0
-----
```

To see how the mean birth weight changes with `sex`, try

```
> stat.table(index = sex, contents = mean(bweight), data=births)
```

```
-----
sex    mean(bweight)
-----
M       3229.90
F       3032.83
-----
```

Add the count to this table. Add the margin with `margin=TRUE`.

```
> stat.table(index = sex, contents = list(count(), mean(bweight)),
+   margin=T, data=births)
```

```
-----
sex    count() mean(bweight)
-----
M       264        3229.90
F       236        3032.83

Total    500        3136.88
-----
```


As an alternative to `bweight` we can look at `lowbw` with

```
> stat.table(index = sex, contents = percent(lowbw), data=births)
```

```
-----
sex    percent(lowbw)
-----
M              100.0
F              100.0
-----
```

All the percentages are 100! To use the `percent` function the variable `lowbw` must also be in the index, as in

```
> stat.table(index = list(sex,lowbw), contents = percent(lowbw), data=births)
```

```
-----
sex    -----lowbw-----
      0      1
-----
M      89.8    10.2
F      86.0    14.0
-----
```

The final column is the percentage of babies with low birth weight by different categories of gestation.

1. Obtain a table showing the frequency distribution of `gest4`.
2. Show how the mean birth weight changes with `gest4`.
3. Show how the percentage of low birth weight babies changes with `gest4`.

```
> stat.table(index = gest4, contents = count(), data=births)
```

```
-----
gest4    count()
-----
[20,35)      31
[35,37)      32
[37,39)     167
[39,45)     260
-----
```

```
> stat.table(index = gest4, contents = mean(bweight), data=births)
```

```
-----
gest4    mean(bweight)
-----
[20,35)      1733.74
[35,37)      2590.31
[37,39)      3093.77
[39,45)      3401.26
-----
```

```
> stat.table(index = list(lowbw,gest4), contents = percent(lowbw), data=births)
```

```
-----
lowbw    -----gest4-----
      [20,35) [35,37) [37,39) [39,45)
-----
0          19.4    59.4    89.2    98.8
1          80.6    40.6    10.8     1.2
-----
```

Another way of obtaining the percentage of low birth weight babies by gestation is to use the `ratio` function:

```
> stat.table(gest4, ratio(lowbw, 1, 100), data=births)
```

```
-----
gest4      ratio(lowbw,
                  1, 100)
-----
[20,35)      80.65
[35,37)      40.62
[37,39)      10.78
[39,45)       1.15
-----
```

This only works because `lowbw` is coded 0/1, with 1 for low birth weight.

Tables of odds can be produced in the same way by using `ratio(lowbw, 1-lowbw)`. The `ratio` function is also very useful for making tables of rates with (say) `ratio(D, Y, 1000)` where `D` is the number of failures, and `Y` is the follow-up time. We shall return to rates in a later practical.

2.3.4 Improving the Presentation of Tables

The `stat.table` function provides default column headings based on the `contents` argument, but these are not always very informative. Supply your own column headings using *tagged* lists as the value of the `contents` argument, within a `stat.table` call:

```
> stat.table(gest4, contents = list( N=count(),
+      "(%)" = percent(gest4)), data=births)
```

```
-----
gest4      N      (%)
-----
[20,35)     31     6.3
[35,37)     32     6.5
[37,39)    167    34.1
[39,45)    260    53.1
-----
```

This improves the readability of the table. It remains to give an informative title to the index variable. You can do this in the same way: instead of giving `gest4` as the `index` argument to `stat.table`, use a named list:

```
> stat.table(index = list("Gestation time" = gest4), data=births)
```

```
-----
Gestation  count()
time
-----
[20,35)      31
[35,37)      32
[37,39)     167
[39,45)     260
-----
```

2.3.5 Two-way Tables

The following call gives a 2×2 table showing the mean birth weight cross-classified by `sex` and `hyp`.

```
> stat.table(list(sex,hyp), contents=mean(bweight), data=births)
```

```
-----hyp-----
sex    normal  hyper
-----
M      3310.75 2814.40
F      3079.50 2699.72
-----
```

Add the count to this table and repeat the function call using `margin = TRUE` to calculate the marginal tables.

```
> stat.table(list(sex,hyp), contents=list(count(), mean(bweight)),
+   margin=T, data=births)
```

```
-----hyp-----
sex    normal  hyper  Total
-----
M      221      43     264
      3310.75 2814.40 3229.90

F      207      29     236
      3079.50 2699.72 3032.83

Total   428      72     500
      3198.90 2768.21 3136.88
-----
```

Use `stat.table` with the `ratio` function to obtain a 2×2 table of percent low birth weight by `sex` and `hyp`.

```
> stat.table(list(sex,hyp), contents=list(count(),mean(bweight)),margin=T, data=births)
```

```
-----hyp-----
sex    normal  hyper  Total
-----
M      221      43     264
      3310.75 2814.40 3229.90

F      207      29     236
      3079.50 2699.72 3032.83

Total   428      72     500
      3198.90 2768.21 3136.88
-----
```

```
> stat.table(list(sex,hyp), contents=list(count(),ratio(lowbw,1,100)),margin=T, data=births)
```

```
-----hyp-----
sex    normal  hyper  Total
-----
```

M	221 6.79	43 27.91	264 10.23
F	207 12.08	29 27.59	236 13.98
Total	428 9.35	72 27.78	500 12.00

You can have fine-grained control over which margins to calculate by giving a logical vector to the `margin` argument. Use `margin=c(FALSE, TRUE)` to calculate margins over `sex` but not `hyp`. This might not be what you expect, but the `margin` argument indicates which of the index variables are to be **marginalized out**, not which index variables are to remain.

2.3.6 Printing

Just like every other R function, `stat.table` produces an object that can be saved and printed later, or used for further calculation. You can control the appearance of a table with an explicit call to `print()`

There are two arguments to the print method for `stat.table`. The `width` argument which specifies the minimum column width, and the `digits` argument which controls the number of digits printed after the decimal point. This table

```
> odds.tab <- stat.table(gest4, list("odds of low bw" = ratio(lowbw,1-lowbw)),
+                          data=births)
> print(odds.tab)
```

gest4	odds of low bw
[20,35)	4.17
[35,37)	0.68
[37,39)	0.12
[39,45)	0.01

shows a table of odds that the baby has low birth weight. Use `width=15` and `digits=3` and see the difference.

```
> print(odds.tab, width=15, digits=3)
```

gest4	odds of low bw
[20,35)	4.167
[35,37)	0.684
[37,39)	0.121
[39,45)	0.012

2.4 Data manipulation with dplyr

2.4.1 Introduction

In this chapter we will reproduce *more or less* the same outputs as in chapter 1.3 using `tidyverse` packages suit.

The main goal is to familiarize you with some of the main `dplyr` and `tidyverse` features. This is an optional practical for participants that have already good basic R basis. All the rest of the course can be done without knowing `dplyr`.

2.4.2 The births data

A quick description of the `births` data-set (from `Epi` package) can be found in chapter 1.3.2. First of all, load the `Epi` and `dplyr` packages. Then we should (re)load the `births` data-set.

```
> library(Epi)
> suppressPackageStartupMessages(library(tidyverse))
> data(births)
```

2.4.3 tibble vs data.frame

Most `dplyr` functions outputs return `tibble` object instead of `data.frame`. Inspect the class and characteristics of the `births` object.

```
> class(births)
[1] "data.frame"
> head(births)
  id bweight lowbw gestwks preterm matage hyp sex
1  1   2974     0   38.52      0     34  0  2
2  2   3270     0    NA     NA     30  0  1
3  3   2620     0   38.15      0     35  0  2
4  4   3751     0   39.80      0     31  0  1
5  5   3200     0   38.89      0     33  1  1
6  6   3673     0   40.97      0     33  0  2
```

Note: This can be summarized using `str` function

```
> str(births)
'data.frame':      500 obs. of  8 variables:
 $ id      : num  1 2 3 4 5 6 7 8 9 10 ...
 $ bweight : num  2974 3270 2620 3751 3200 ...
 $ lowbw   : num  0 0 0 0 0 0 0 0 0 0 ...
 $ gestwks : num  38.5 NA 38.2 39.8 38.9 ...
 $ preterm : num  0 NA 0 0 0 0 0 0 0 0 ...
 $ matage  : num  34 30 35 31 33 33 29 37 36 39 ...
 $ hyp     : num  0 0 0 0 1 0 0 0 0 0 ...
 $ sex     : num  2 1 2 1 1 2 2 1 2 1 ...
```

`births` object is a 500 x 8 `data.frame`.

Let's convert `births` to `tibble` format with `as_tibble` function.

```

> births_tbl <- as_tibble(births)
> class(births_tbl)
[1] "tbl_df"      "tbl"        "data.frame"
> births_tbl
# A tibble: 500 × 8
   id bweight lowbw gestwks preterm matage hyp sex
  <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <dbl>
1     1  2974     0  38.5     0    34     0     2
2     2  3270     0   NA     NA    30     0     1
3     3  2620     0  38.2     0    35     0     2
4     4  3751     0  39.8     0    31     0     1
5     5  3200     0  38.9     0    33     1     1
6     6  3673     0  41.0     0    33     0     2
7     7  3628     0  42.1     0    29     0     2
8     8  3773     0  40.2     0    37     0     1
9     9  3960     0  42.0     0    36     0     2
10    10  3405     0  39.3     0    39     0     1
# & 490 more rows
> ## another way to visualize data set is to use glimpse function
> glimpse(births_tbl)
Rows: 500
Columns: 8
$ id      <dbl> 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,...
$ bweight <dbl> 2974, 3270, 2620, 3751, 3200, 3673, 3628, 3773, 3960, 3405, 40...
$ lowbw   <dbl> 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,...
$ gestwks <dbl> 38.52, NA, 38.15, 39.80, 38.89, 40.97, 42.14, 40.21, 42.03, 39...
$ preterm <dbl> 0, NA, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0...
$ matage  <dbl> 34, 30, 35, 31, 33, 33, 29, 37, 36, 39, 37, 35, 38, 34, 28, 38...
$ hyp     <dbl> 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,...
$ sex     <dbl> 2, 1, 2, 1, 1, 2, 2, 1, 2, 1, 1, 2, 2, 1, 2, 1, 2, 1, 2, 2,...

```

As you can see `tibble` inherits from `data.frame` which implies that all functions working with `data.frame` objects will work with `tibble` objects. The opposite is not necessary true. `tibble` has a couple of extra features compared to classical `data.frame`. One of them is a slightly more user-friendly console print. The main differences being that `tibble` objects supports grouping/nesting features. Some examples we be done will see latter on.

2.4.4 Piping functions

This is one of the most popular features of `tidyverse` grammar. It enables function chaining in R. Function outputs are passed as input to the following function and so on. It can help to make the code more readable. Here is an example of classic vs piped functions.

```

> head(births, 4)
   id bweight lowbw gestwks preterm matage hyp sex
1  1  2974     0  38.52     0    34     0     2
2  2  3270     0   NA     NA    30     0     1
3  3  2620     0  38.15     0    35     0     2
4  4  3751     0  39.80     0    31     0     1
> births %>% head(4)
   id bweight lowbw gestwks preterm matage hyp sex
1  1  2974     0  38.52     0    34     0     2
2  2  3270     0   NA     NA    30     0     1
3  3  2620     0  38.15     0    35     0     2
4  4  3751     0  39.80     0    31     0     1

```

Note: By default the chained object is given as the first argument to the following function. You can use `.` if this is not the case.

Here is a dummy example where we do not give the first argument to a function but the second one.

```
> 4 %>% head(births, .)
  id bweight lowbw gestwks preterm matage hyp sex
1  1   2974     0   38.52     0     34  0  2
2  2   3270     0    NA     NA     30  0  1
3  3   2620     0   38.15     0     35  0  2
4  4   3751     0   39.80     0     31  0  1
```

2.4.5 mutate columns

`mutate` will allow you to add and or modify columns in a `data.frame`.

Let's create 2 new variables :

- `agegrp` (5 years mother's age group)
- `gest4` (gestation time split in 4 categories)

And modify 2 others:

- `hyp` (factor version of `hyp`; normal vs hyper)
- `sex` (factor version of `sex`; M vs F)

```
> births_tbl <-
+   births_tbl %>%
+   mutate(
+     ## modify hyp variable (conversion into factor)
+     hyp = factor(hyp, levels = c(0, 1), labels = c("normal", "hyper")),
+     ## creating a new variable agegrp
+     agegrp = cut(matage, breaks = c(20, 25, 30, 35, 40, 45), right = FALSE),
+     ## modify sex variable (conversion into factor)
+     sex = factor(sex, levels = c(1, 2), labels = c("M", "F")),
+     ## creating a new variable gest4 with case_when instead of cut
+     gest4 =
+       case_when(
+         gestwks < 25 ~ 'less than 25 weeks',
+         gestwks >= 25 & gestwks < 30 ~ '25-30 weeks',
+         gestwks >= 30 & gestwks < 35 ~ '30-35 weeks',
+         gestwks >= 35 & gestwks < 40 ~ '35-40 weeks',
+         gestwks >= 40 ~ 'more than 40 weeks'
+       )
+   )
> births_tbl
# A tibble: 500 × 10
  id bweight lowbw gestwks preterm matage hyp sex agegrp gest4
<dbl> <dbl> <dbl> <dbl> <dbl> <dbl> <fct> <fct> <fct> <chr>
1 1 2974 0 38.5 0 34 normal F [30,35) 35-40 weeks
2 2 3270 0 NA NA 30 normal M [30,35) <NA>
3 3 2620 0 38.2 0 35 normal F [35,40) 35-40 weeks
4 4 3751 0 39.8 0 31 normal M [30,35) 35-40 weeks
```

```

5      5      3200      0      38.9      0      33 hyper M      [30,35) 35-40 weeks
6      6      3673      0      41.0      0      33 normal F      [30,35) more than 40...
7      7      3628      0      42.1      0      29 normal F      [25,30) more than 40...
8      8      3773      0      40.2      0      37 normal M      [35,40) more than 40...
9      9      3960      0      42.0      0      36 normal F      [35,40) more than 40...
10     10      3405      0      39.3      0      39 normal M      [35,40) 35-40 weeks
# < 490 more rows

```

You can see in the table columns header the type of data contained in each column. For instance `<dbl>` stands for double (i.e. numeric value) and `<fct>` stands for factor. In R `data.frame` (/ `tibble`) data type have to be the same within a column (e.g. numeric only) but can be of different type across columns.

Notes than `case_when` function do not return a `factor` but a `character` variable in this case. You will have to force the conversion to `factor` if needed.

2.4.6 select columns, filter and arrange rows

`select` is used for column sub-setting while `filter` is for row sub-setting. They are equivalent to the `[]` in R base language.

Let's display a table where only babies' `id`, `sex`, `bweight` and mothers' `agegrp` are kept for babies with a `bweight` grater than 4000g.

```

> births_tbl %>%
+   ## select only id, women age group, sex and birth weight of the baby
+   select(id, agegrp, sex, bweight) %>%
+   ## keep only babies weighing more than 4000g
+   filter(bweight > 4000)
# A tibble: 30 × 4
   id agegrp sex  bweight
  <dbl> <fct> <fct>   <dbl>
1    11 [35,40) M     4020
2    31 [30,35) F     4022
3    57 [25,30) M     4501
4    78 [35,40) M     4512
5    86 [30,35) M     4141
6    87 [30,35) M     4071
7    92 [30,35) F     4027
8   122 [30,35) M     4092
9   139 [35,40) M     4069
10  170 [40,45) M     4057
# < 20 more rows

```

`select` can also be useful to reorder and rename columns.

`arrange` is a nice feature to reorder observations according to chosen attributes.

Let's rename `agegrp`, `sex` and `bweight` with more explicit labels and reorder the table according to babies' decreasing birth weight.

```

> births_tbl %>%
+   ## select only id, women age group, sex and birth weight of the baby
+   select(
+     id,
+     'Age group' = agegrp,
+     Sex = sex,
+     'Birth weight' = bweight
+   )

```



```
+ ) %>%
+ ## rearrange rows to put the heaviest newborn on top
+ arrange(desc(`Birth weight`))

# A tibble: 500 × 4
  id `Age group` Sex   `Birth weight`
  <dbl> <fct>      <fct>         <dbl>
1   319 [30,35)    M             4553
2   474 [25,30)    M             4516
3    78 [35,40)    M             4512
4    57 [25,30)    M             4501
5   238 [25,30)    M             4436
6   288 [30,35)    M             4423
7   206 [40,45)    M             4340
8   355 [35,40)    M             4319
9   459 [30,35)    M             4304
10  469 [30,35)    F             4300
# ℹ 490 more rows
```

Note: `tibble` supports blank spaces in the column names which can be handy for final table rendering. When you want to work with columns with blank spaces, do not forget to use the “ (back-quote).

Let's do the same but arranging the table by decreasing birth weights within each sex.

```
> births_tbl %>%
+ ## select only id, women age group, sex and birth weight of the baby
+ select(
+   id,
+   `Age group` = agegrp,
+   Sex = sex,
+   `Birth weight` = bweight
+ ) %>%
+ ## rearrange rows to put the heaviest newborn on top
+ arrange(Sex, desc(`Birth weight`))

# A tibble: 500 × 4
  id `Age group` Sex   `Birth weight`
  <dbl> <fct>      <fct>         <dbl>
1   319 [30,35)    M             4553
2   474 [25,30)    M             4516
3    78 [35,40)    M             4512
4    57 [25,30)    M             4501
5   238 [25,30)    M             4436
6   288 [30,35)    M             4423
7   206 [40,45)    M             4340
8   355 [35,40)    M             4319
9   459 [30,35)    M             4304
10  387 [35,40)    M             4287
# ℹ 490 more rows
```

2.4.7 group_by and summarise data

One of the most valuable features of `dplyr` is the ability to aggregate data sharing a common attribute to process by group operations.

Here we want to compute the number of boys and girls in the data-set.

The idea here is to split the `births` table in 2. One for boys, the other for girls and to count

the number of rows of each sub-table.

```
> births.01 <-
+   births_tbl %>%
+   ## group the data according to the sex attribute
+   group_by(sex) %>%
+   ## count the number of rows/individuals in each group
+   summarise(
+     count = n()
+   )
> births.01
# A tibble: 2 × 2
  sex    count
<fct> <int>
1 M         264
2 F         236
```

Note: `n` function is equivalent to `nrow`

Now we have the number of boys and girls, we can compute the percentage of newborns in each sex group.

```
> births.02 <-
+   births.01 %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )
```

Trick: most of `dplyr` functions can be applied with an embedded condition using `across` function. This can be very handy in some cases.

As an illustration if you want to calculate the `sum` of every `birth.02` numerical columns

```
> births.03 <-
+   births_tbl %>%
+   select(gest4, sex, gestwks, bweight, matage) %>%
+   group_by(gest4, sex) %>%
+   summarise(
+     across(
+       where(is.numeric),
+       ~ mean(.x, na.rm = TRUE)
+     ),
+     .groups = 'drop'
+   )
> births.03
# A tibble: 11 × 5
  gest4          sex  gestwks bweight matage
  <chr>      <fct>   <dbl>   <dbl>   <dbl>
1 25-30 weeks M        28.0    1000     30
2 25-30 weeks F        27.1     668    29.5
3 30-35 weeks M        33.3   2224.    32.8
4 30-35 weeks F        32.8   1672.     33
5 35-40 weeks M        38.5   3178.    34.3
6 35-40 weeks F        38.5   3055.    34.1
7 less than 25 weeks F        24.7     864     40
8 more than 40 weeks M        40.7   3612.    34.4
9 more than 40 weeks F        40.8   3376.    33.8
10 <NA>      M        NaN    3056.     33
11 <NA>      F        NaN    3188.     31
```

`across` function supports the purrr-style lambda format, e.g. `mean(.x, na.rm = TRUE)` where `.x` refers to the values from the data set to be passed to the function.

Some other functions ending by `_with` can be used conditionally within `dplyr`. As an example we can rename only columns which are not numeric at once (here we want to make all column names using upper characters) using the combination of `rename_with` and `where`.

```
> births.03 %>%
+   rename_with(toupper, where(~ !is.numeric(.x)))

# A tibble: 11 × 5
  GEST4      SEX gestwks bweight matage
  <chr>    <fct>   <dbl>   <dbl> <dbl>
1 25-30 weeks M      28.0    1000    30
2 25-30 weeks F      27.1     668    29.5
3 30-35 weeks M      33.3   2224.    32.8
4 30-35 weeks F      32.8   1672.    33
5 35-40 weeks M      38.5   3178.    34.3
6 35-40 weeks F      38.5   3055.    34.1
7 less than 25 weeks F      24.7     864    40
8 more than 40 weeks M      40.7   3612.    34.4
9 more than 40 weeks F      40.8   3376.    33.8
10 <NA>      M      NaN    3056.    33
11 <NA>      F      NaN    3188.    31
```

Let's now compute the number of births and the mean birth weight according to newborn gender.

```
> births.05 <-
+   births_tbl %>%
+   group_by(sex) %>%
+   summarise(
+     count = n(),
+     bweight.mean = mean(bweight)
+   )
> births.05

# A tibble: 2 × 3
  sex    count bweight.mean
  <fct> <int>    <dbl>
1 M      264    3230.
2 F      236    3033.
```

With `births.05` table, compute the global mean new birth weight.

Note: with such a table the mean baby's birth weight have to be weighted by number of boys and girls.

```
> births.05 %>%
+   summarise(
+     count.tot = sum(count),
+     bweight.mean.tot = weighted.mean(bweight.mean, count)
+   )

# A tibble: 1 × 2
  count.tot bweight.mean.tot
  <int>    <dbl>
1     500    3137.
```

```

> # this is equivalent to
> births_tbl %>%
+   summarise(
+     count.tot = n(),
+     bweight.mean.tot = mean(bweight)
+   )
# A tibble: 1 × 2
  count.tot bweight.mean.tot
  <int>      <dbl>
1       500        3137.

```

2.4.8 Multiple grouping

In some cases, we can be interested in looking at more than a single strata. This can be achieved using multiple grouping.

Let's count the number of people per gender and birth weight class (low vs not low)

```

> births.06 <-
+   births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n()
+   )
> births.06
# A tibble: 4 × 3
# Groups:   sex [2]
  sex    lowbw count
  <fct> <dbl> <int>
1 M         0    237
2 M         1     27
3 F         0   203
4 F         1     33

```

Try then to compute the percentage of people in each group.

Look at the difference between the 2 following command lines:

```

> births.06 %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )
# A tibble: 4 × 4
# Groups:   sex [2]
  sex    lowbw count percent
  <fct> <dbl> <int>   <dbl>
1 M         0    237    89.8
2 M         1     27    10.2
3 F         0   203    86.0
4 F         1     33    14.0

> births.06 %>%
+   ungroup() %>%
+   mutate(
+     percent = count / sum(count) * 100
+   )

```

```
# A tibble: 4 × 4
  sex    lowbw count percent
<fct> <dbl> <int>   <dbl>
1 M         0   237    47.4
2 M         1    27     5.4
3 F         0   203    40.6
4 F         1    33     6.6
```

Note: summarizing a data-set will remove the latest level of grouping but not the deeper ones if multiple grouping has been done. In some cases you might have to explicitly ungroup your `data.frame` before doing calculations. In the previous examples, if you do not ungroup the data-set, percentages are computed per gender. Ungrouping will let you compute the overall percentages.

Trick: a good practice is to ungroup all the summarized dataset in order to prevent form confusion. You can do it using the `.group = 'drop'` option in `summarize()`.

```
> ## this tibble will still be grouped by sex
> births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n()
+   )
# A tibble: 4 × 3
# Groups:   sex [2]
  sex    lowbw count
<fct> <dbl> <int>
1 M         0   237
2 M         1    27
3 F         0   203
4 F         1    33

> ## this tibble will be group free
> births_tbl %>%
+   group_by(sex, lowbw) %>%
+   summarise(
+     count = n(),
+     .groups = 'drop'
+   )
# A tibble: 4 × 3
  sex    lowbw count
<fct> <dbl> <int>
1 M         0   237
2 M         1    27
3 F         0   203
4 F         1    33
>
>
```

The same exercise can be done using gestation time group (`gest4`) as stratifying variable. Lets compute number and mean birth weights according to gestation time category

```
> births_tbl %>%
+   group_by(gest4) %>%
+   summarise(
+     count = n(),
+     bweight.mean = mean(bweight)
+   )
```

```
# A tibble: 6 × 3
  gest4          count bweight.mean
  <chr>          <int>      <dbl>
1 25-30 weeks         4         834
2 30-35 weeks        26        1906.
3 35-40 weeks       322        3122.
4 less than 25 weeks   1         864
5 more than 40 weeks  137        3493.
6 <NA>              10        3082.
```

Birth weight increases with gestation time.

We can also spot that in our data-set the gestation time is missing for 10 newborns. We will remove this observation for the rest of the practical session.

Lets cross-tabulate the birth weight category and the gestation time groups.

```
> births_tbl %>%
+   ## keep only the newborn with defined gestational time category
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(lowbw, gest4) %>%
+   ## compute the number of babies in each cross category
+   summarise(
+     count = n()
+   ) %>%
+   ## compute the percentage of babies in each gestational time category per
+   ## birth weight category
+   mutate(
+     percent = count / sum(count, na.rm = TRUE)
+   )
# A tibble: 8 × 4
# Groups:   lowbw [2]
  lowbw gest4          count percent
  <dbl> <chr>          <int>      <dbl>
1     0 30-35 weeks         6  0.0139
2     0 35-40 weeks       289  0.671
3     0 more than 40 weeks  136  0.316
4     1 25-30 weeks         4  0.0678
5     1 30-35 weeks        20  0.339
6     1 35-40 weeks        33  0.559
7     1 less than 25 weeks   1  0.0169
8     1 more than 40 weeks   1  0.0169
```

Similarly we can be interested in the birth weight distribution per gestational time.

```
> births_tbl %>%
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(gest4, lowbw) %>%
+   summarise(
+     count = n()
+   ) %>%
+   ## compute the percentage of babies in each birth weight category per gestational
+   ## time category
+   mutate(
+     percent = count / sum(count, na.rm = TRUE)
+   )
```

```
# A tibble: 8 × 4
# Groups:   gest4 [5]
  gest4          lowbw count percent
  <chr>         <dbl> <int>   <dbl>
1 25-30 weeks      1      4 1
2 30-35 weeks      0      6 0.231
3 30-35 weeks      1     20 0.769
4 35-40 weeks      0    289 0.898
5 35-40 weeks      1     33 0.102
6 less than 25 weeks 1      1 1
7 more than 40 weeks 0    136 0.993
8 more than 40 weeks 1      1 0.00730
```

Note: grouping order matters! and can be confusing so think about ungrouping intermediate tables.

2.4.9 Bind and join tables

Another nice feature of `dplyr` is tables binding and joining functions. To practice we will create 2 fake tibble:

- **age** an individual database which contains `pid` (unique individuals id) and `age` in year
- **center** an study center database which contains `pid` (unique individuals id) and `center` (the center where an individual is registered)

```
> age <-
+   tibble(
+     pid = 1:6,
+     age = sample(15:25, size = 6, replace = TRUE)
+   )
> center <-
+   tibble(
+     pid = c(1, 2, 3, 4, 10),
+     center = c('A', 'B', 'A', 'B', 'C')
+   )
> age
# A tibble: 6 × 2
  pid   age
  <int> <int>
1     1    24
2     2    21
3     3    22
4     4    16
5     5    16
6     6    25
> center
# A tibble: 5 × 2
  pid center
  <dbl> <chr>
1     1 A
2     2 B
3     3 A
4     4 B
5    10 C
```

Now the tables are define we will try to make the linkage between individuals ages and the center they belong to.

First of all let's have a look to `bind_rows` function.

```
> bind_rows(age, center)
# A tibble: 11 × 3
  pid   age center
<dbl> <int> <chr>
1     1    24 <NA>
2     2    21 <NA>
3     3    22 <NA>
4     4    16 <NA>
5     5    16 <NA>
6     6    25 <NA>
7     1     NA  A
8     2     NA  B
9     3     NA  A
10    4     NA  B
11   10     NA  C
```

Is it useful?

Here not really but that can be in other situations (e.g. several individuals data base to merge..).

Note: in `bind_rows`, if columns names do not match, they are fill with NA.

Here we want to join the 2 `tibble` according to the common attribute `pid`. Depending on the context you can be interested in joining tables differently. Have a look at the differences between `left_join`, `full_join` and `inner_join`.

```
> ## all individuals from ages are kept
> left_join(age, center, by = c('pid'))
# A tibble: 6 × 3
  pid   age center
<dbl> <int> <chr>
1     1    24  A
2     2    21  B
3     3    22  A
4     4    16  B
5     5    16 <NA>
6     6    25 <NA>

> ## everithing is kept
> full_join(age, center, by = c('pid'))
# A tibble: 7 × 3
  pid   age center
<dbl> <int> <chr>
1     1    24  A
2     2    21  B
3     3    22  A
4     4    16  B
5     5    16 <NA>
6     6    25 <NA>
7    10     NA  C

> ## only the individuals present in both dataset are kept
> inner_join(age, center, by = c('pid'))
```



```
# A tibble: 4 × 3
  pid   age center
<dbl> <int> <chr>
1     1    24 A
2     2    21 B
3     3    22 A
4     4    16 B
```

Can you spot the differences between the commands above?

As an exercise, you can try to compute the individuals' mean age per center.

```
> inner_join(age, center, by = c('pid')) %>%
+   group_by(center) %>%
+   summarise(
+     mean_age = mean(age)
+   )

# A tibble: 2 × 2
  center mean_age
<chr>      <dbl>
1 A          23
2 B         18.5
```

Note: the `by` argument indicates which column should be used to make the join. In some cases, you might have to use several columns to match (e.g. per sex and age group), this can be easily done specifying a vector of column names.

2.4.10 Data Visualization with ggplot2

One of the packages that have contributed to **tidyverse** success is for sure **ggplot2**. We will go more into the details on how to produce graphs with **ggplot2** in another practical. Just a quick example of graphic using **ggplot2**.

Let's Create a bar plot to visualize the number of births by women age group.

First you have to create a table with the number of birth per age group.

```
> birth_per_ageg <- births_tbl %>% group_by(agegrp) %>% summarise(total_births = n())

> (gg.01 <-
+   ggplot(birth_per_ageg, aes(x = agegrp, y = total_births)) +
+   geom_bar(stat = "identity"))
```

This graph can be customized adding labels and title to the plot:

```
> (gg.02 <-
+   gg.01 +
+   xlab("Women Age Group") +
+   ylab("Total Births") +
+   ggtitle("Number of Births per Women Age Group"))
```

As you can see, plots from **ggplot** family are built sequentially using the `+` operator for each additional element.

2.4.11 String manipulation with stringr

Another popular tidyverse popular package is **stringr** package. This package is specialized in the string manipulation. Here are couple of examples.

Let's create a character vector with the following elements representing country names: "Estonia", "Finland", "Denmark", "United Kingdom".

```
> countries <- c("Estonia", "Finland", "Denmark", "United Kingdom")
```

Extract the first three characters from each country name:

```
> country_initials <- str_sub(countries, start = 1, end = 3)
```

Convert all country names to uppercase:

```
> countries_upper <- str_to_upper(countries)
```

Replace "United" with "Utd" in each country name:

```
> countries_modified <- str_replace(countries, "United", "Utd")
```

Find the positions of the letter "n" in each country name:

```
> a_positions <- str_locate_all(countries, "n")
```

As you can see, the output of **str_locate_all** is a list (one element per character string) containing a 2 column table with one line for each match. The first column (start) being the position of the beginning of the match and the second one (end) being the end of the match. In our case, since we are searching for a single character match, this 2 indexes are always the same.

Count the number of characters in each country name:

```
> character_counts <- str_length(countries)
```

These examples demonstrate various string manipulation operations using the **stringr** package. You can modify the exercises, combine several operations or explore other string manipulation functions provided by **stringr** to further practice and enhance your skills in manipulating and analyzing text data.

2.4.12 purrrr package to apply functions to list

Among my favorite tidyverse packages, you will find **purrr**. This package contains several functions that are very similar to **lapply** function.

The simplest example could be to apply the same function to a list of elements. As an example let's add "country: " in front of all our

Apply a function to each element of the vector using **map()**. Here producing the mean of some grades per class:

```
> grades <-  
+   list(  
+     c1 = c(80, 85, 90),  
+     c2 = c(75, 70, 85, 88),  
+     c3 = c(90, 85, 95)  
+   )  
> mean_grades <- map(grades, mean)
```

By default `map()` return a list. One of the nice feature of **purrr** functions is to be able to specify the type of output you want (e.g. `_dbl` for numeric, `_chr` for characters, ...). Check and try to explain the differences between the following command lines:

```
> map(grades, mean)
$c1
[1] 85

$c2
[1] 79.5

$c3
[1] 90

> map_dbl(grades, mean)
   c1   c2   c3
85.0 79.5 90.0

> map_chr(grades, mean)
   c1         c2         c3
"85.000000" "79.500000" "90.000000"

> map_df(grades, mean)
# A tibble: 1 × 3
   c1    c2    c3
<dbl> <dbl> <dbl>
1    85  79.5   90
```

Other nice features of `map` like functions is the availability to support more than one argument. `map2()` for 2 arguments and `pmap()` for more than 2. This can be very handy in some conditions. If you are interested you can have a look to this function help file and play with the examples.

purrr package has also a set of functions that can be used to apply iteratively a function using `reduce` and/or `accumulate`. The 2 functions behave the same way, it takes the 2 first element of a list, apply a function. The results of the first operation is combined with the third element of the list in the same function and so on.. The only difference is that `accumulate` return intermediate results while `reduce` return only the final results.

Here an example of the cumulative product of the 10 first numbers.

```
> 1:10 %>% reduce(`*`)
[1] 3628800

> 1:10 %>% accumulate(`*`)
   [1]      1      2      6     24    120    720   5040  40320 362880
  [10] 3628800
```

2.4.13 Bonus: Rendering tables

Once you have produced a nice data-set we can be interested in rendering it in a nice format that can meet presentation/publication expectations. The **kableExtra** table can be useful to achieve this goal.

```

> # if(!require(kableExtra)) install.packages('kableExtra')
> library(kableExtra)
> births.08 <-
+   births_tbl %>%
+   filter(
+     !is.na(gest4)
+   ) %>%
+   group_by(gest4) %>%
+   summarise(
+     N = n()
+   ) %>%
+   mutate(
+     `(`) = (N / sum(N)) %>% scales::percent()
+   )
> ## default
> births.08
# A tibble: 5 × 3
  gest4      N `(`)
  <chr>    <int> <chr>
1 25-30 weeks      4 0.82%
2 30-35 weeks     26 5.31%
3 35-40 weeks    322 65.71%
4 less than 25 weeks    1 0.20%
5 more than 40 weeks   137 27.96%

> ## markdown flavor (useful fo automatic report production with knitr)
> # births.08 %>%
> #   knitr::kable(format = 'markdown')
>
> ## create an html version of the table and save it on the hard drive
> births.08 %>%
+   kable() %>%
+   kable_styling(
+     bootstrap_options = c("striped", "hover", "condensed", "responsive"),
+     full_width = FALSE
+   ) %>%
+   save_kable(file = 'births.08.html', self_contained = TRUE)

```

2.5 Graphics in R

There are three kinds of plotting functions in R:

1. Functions that generate a new plot, e.g. `hist()` and `plot()`.
2. Functions that add extra things to an existing plot, e.g. `lines()` and `text()`.
3. Functions that allow you to interact with the plot, e.g. `locator()` and `identify()`.

The normal procedure for making a graph in R is to make a fairly simple initial plot and then add on points, lines, text etc., preferably in a script.

2.5.1 Simple plot on the screen

Load the births data and get an overview of the variables:

```
> library( Epi )
> data( births )
> str( births )
```

Now look at the birthweight distribution with

```
> hist(births$bweight)
```

The histogram can be refined – take a look at the possible options with

```
> help(hist)
```

and try some of the options, for example:

```
> hist(births$bweight, col="gray", border="white")
```

To look at the relationship between birthweight and gestational weeks, try

```
> with(births, plot(gestwks, bweight))
```

You can change the plot-symbol by the option `pch=`. If you want to see all the plot symbols try:

```
> plot(1:25, pch=1:25)
```

4. Make a plot of the birth weight versus maternal age with

```
> with(births, plot(matage, bweight) )
```

5. Label the axes with

```
> with(births, plot(matage, bweight, xlab="Maternal age", ylab="Birth weight (g)" ) )
```

2.5.2 Colours

There are many colours recognized by R. You can list them all by `colours()` or, equivalently, `colors()` (R allows you to use British or American spelling). To colour the points of birthweight versus gestational weeks, try

```
> with(births, plot(gestwks, bweight, pch=16, col="green") )
```

This creates a solid mass of colour in the centre of the cluster of points and it is no longer possible to see individual points. You can recover this information by overwriting the points with black circles using the `points()` function.

```
> with(births, points(gestwks, bweight, pch=1) )
```

Note: when the number of data points on a scatter plot is large, you may also want to decrease the point size: to get points that are 50% of the original size, add the parameter `cex=0.5` (or another number <1 for different sizes).

2.5.3 Adding to a plot

The `points()` function just used is one of several functions that add elements to an existing plot. By using these functions, you can create quite complex graphs in small steps.

Suppose we wish to recreate the plot of birthweight *vs* gestational weeks using different colours for male and female babies. To start with an empty plot, try

```
> with(births, plot(gestwks, bweight, type="n"))
```

Then add the points with the `points` function.

```
> with(births, points(gestwks[sex==1], bweight[sex==1], col="blue"))
> with(births, points(gestwks[sex==2], bweight[sex==2], col="red"))
```

To add a legend explaining the colours, try

```
> legend("topleft", pch=1, legend=c("Boys", "Girls"), col=c("blue", "red"))
```

which puts the legend in the top left hand corner.

Finally we can add a title to the plot with

```
> title("Birth weight vs gestational weeks in 500 singleton births")
```

2.5.3.1 Using indexing for plot elements

One of the most powerful features of R is the possibility to index vectors, not only to get subsets of them, but also for repeating their elements in complex sequences.

Putting separate colours on males and female as above would become very clumsy if we had a 5 level factor instead of sex.

Instead of specifying one color for all points, we may specify a vector of colours of the same length as the `gestwks` and `bweight` vectors. This is rather tedious to do directly, but R allows you to specify an expression anywhere, so we can use the fact that `sex` takes the values 1 and 2, as follows:

First create a colour vector with two colours, and take look at `sex`:

```
> c("blue","red")
> births$sex
```

Now see what happens if you index the colour vector by sex:

```
> c("blue","red")[births$sex]
```

For every occurrence of a 1 in `sex` you get "blue", and for every occurrence of 2 you get "red", so the result is a long vector of "blue"s and "red"s corresponding to the males and females. This can now be used in the plot:

```
> with(births, plot( gestwks, bweight, pch=16, col=c("blue","red")[sex]) )
```

The same trick can be used if we want to have a separate symbol for mothers over 40 say. We first generate the indexing variable:

```
> births$oldmum <- ( births$matage >= 40 ) + 1
```

Note we add 1 because (`matage >= 40`) generates a logic variable, so by adding 1 we get a numeric variable with values 1 and 2, suitable for indexing:

```
> with(births, plot( gestwks, bweight, pch=c(16,3)[oldmum], col=c("blue","red")[sex] ))
```

so where `oldmum` is 1 we get `pch=16` (a dot) and where `oldmum` is 2 we get `pch=3` (a cross).

R will accept any kind of complexity in the indexing as long as the result is a valid index, so you don't need to create the variable `oldmum`, you can create it on the fly:

```
> with(births, plot( gestwks, bweight, pch=c(16,3)[(matage>=40)+1], col=c("blue","red")[sex] ))
```

2.5.3.2 Generating colours

R has functions that generate a vector of colours for you. For example,

```
> rainbow(4)
```

produces a vector with 4 colours (not immediately human readable, though). There are a few other functions that generates other sequences of colours, type `?rainbow` to see them. The `color` function (or `colour` function if you prefer) returns a vector of the colour names that R knows about. These names can also be used to specify colours.

Gray-tones are produced by the function `gray` (or `grey`), which takes a numerical argument between 0 and 1; `gray(0)` is black and `gray(1)` is white. Try:

```
> plot( 0:10, pch=16, cex=3, col=gray(0:10/10) )
> points( 0:10, pch=1, cex=3 )
```

2.5.4 Saving your graphs for use in other documents

If you need to use the plot in a report or presentation, you can save it in a graphics file. Once you have generated the script (sequence of R commands) that produce the graph (and it looks ok on screen), you can start a non-interactive graphics device and then re-run the script.

Instead of appearing on the screen, the plot will now be written directly to a file. After the plot has been completed you will need to close the device again in order to be able to access the file. Try:

```
> pdf(file="bweight_gwks.pdf", height=4, width=4)
> with(births, plot( gestwks, bweight, col=c("blue","red")[sex]) )
> legend("topleft", pch=1, legend=c("Boys","Girls"), col=c("blue","red"))
> dev.off()
```

This will give you a portable document file `bweight_gwks.pdf` with a graph which is 4 inches tall and 4 inches wide.

Instead of *pdf*, other formats can be used (*jpg*, *png*, *tiff*, ...). See `help(Devices)` for the available options.

In window-based environments (R GUI for Windows, R-Studio) you may also use the menu (`File` → `Save as` ... or `Export`) to save the active graph as a file and even copy-paste may work (from R graphics window to Word, for instance) – however, writing it manually into the file is recommended for reproducibility purposes (in case you need to redraw your graph with some modifications).

2.5.5 The `par()` command

It is possible to manipulate any element in a graph, by using the graphics options. These are collected on the help page of `par()`. For example, if you want axis labels always to be horizontal, use the command `par(las=1)`. This will be in effect until a new graphics device is opened.

Look at the typewriter-version of the help-page with

```
> help(par)
```

or better, use the the html-version through `Help` → `Html help` → `Packages` → `graphics` → `P` → `par`.

It is a good idea to take a print of this (having set the text size to “smallest” because it is long) and carry it with you at any time to read in buses, cinema queues, during boring lectures etc. Don’t despair, few R-users can understand what all the options are for.

`par()` can also be used to ask about the current plot, for example `par("usr")` will give you the exact extent of the axes in the current plot.

If you want more plots on a single page you can use the command

```
> par( mfrow=c(2,3) )
```

This will give you a layout of 2 rows by 3 columns for the next 6 graphs you produce. The plots will appear by row, i.e. in the top row first. If you want the plots to appear columnwise, use `par(mfcol=c(2,3))` (you still get 2 rows by 3 columns).

To restore the layout to a single plot per page use

```
> par(mfrow=c(1,1))
```

If you want a more detailed control over the layout of multiple graphs on a single page look at `?layout`.

2.5.6 Interacting with a plot

The `locator()` function allows you to interact with the plot using the mouse. Typing `locator(1)` shifts you to the graphics window and waits for one click of the left mouse button. When you click, it will return the corresponding coordinates.

You can use `locator()` inside other graphics functions to position graphical elements exactly where you want them. Recreate the birth-weight plot,

```
> with(births, plot(gestwks, bweight, col = c("blue", "red")[sex]) )
```

and then add the legend where you wish it to appear by typing

```
> legend(locator(1), pch=1, legend=c("Boys", "Girls"), col=c("blue", "red") )
```

The `identify()` function allows you to find out which records in the data correspond to points on the graph. Try

```
> with(births, identify(gestwks, bweight))
```

When you click the left mouse button, a label will appear on the graph identifying the row number of the nearest point in the data frame `births`. If there is no point nearby, R will print a warning message on the console instead. To end the interaction with the graphics window, right click the mouse: the `identify` function returns a vector of identified points.

1. Use `identify()` to find which records correspond to the smallest and largest number of gestational weeks and view the corresponding records:

```
> with(births, births[identify(gestwks, bweight), ])
```

2.6 Simple simulation

Monte Carlo methods are computational procedures dealing with simulation of artificial data from given probability distributions with the purpose of learning about the behaviour of phenomena involving random variability. These methods have a wide range of applications in statistics as well as in several branches of science and technology. By solving the following exercises you will learn to use some basic tools of statistical simulation.

1. Whenever using a *random number generator* (RNG) for a simulation study (or for another purpose, such as for producing a randomization list to be used in a clinical trial or for selecting a random sample from a large cohort), it is a good practice to set first the *seed*. It is a number that determines the initial state of the RNG, from which it starts creating the desired sequence of pseudo-random numbers. Explicit specification of the seed enables the reproducibility of the sequence. – Instead of the number 5462319 below you may use your own seed of choice.

```
> set.seed(5462319)
```

2. Generate a random sample of size 20 from a normal distribution with mean 100 and standard deviation 10. Draw a histogram of the sampled values and compute the conventional summary statistics

```
> x <- rnorm(20, 100, 10)
> hist(x)
> c(mean(x), sd(x))
```

Repeat the above lines and compare the results.

```
> x <- rnorm(20, 100, 10)
> hist(x)
> c(mean(x), sd(x))
```

3. Now replace the sample size 20 by 1000 and run again twice the previous command lines with this size but keeping the parameter values as before. Compare the results between the two samples here as well as with those in the previous item.

```
> x <- rnorm(1000, 100, 10)
> hist(x)
> c(mean(x), sd(x))
```

```
> x <- rnorm(1000, 100, 10)
> hist(x)
> c(mean(x), sd(x))
```

4. Generate 500 observations from a Bernoulli(p) distribution, or Bin(1, p) distribution, taking values 1 and 0 with probabilities p and $1 - p$, respectively, when $p = 0.4$:

```
> X <- rbinom(500, 1, 0.4)
> table(X)
```

5. Now generate another 0/1 variable Y , being dependent on previously generated X , so that $P(Y = 1|X = 1) = 0.2$ and $P(Y = 1|X = 0) = 0.1$.

```
> Y <- rbinom(500,1,0.1*X+0.1)
> table(X,Y)
> prop.table(table(X,Y),1)
```

6. Generate data obeying a simple linear regression model $y_i = 5 + 0.1x_i + \varepsilon_i$, $i = 1, \dots, 100$, in which $\varepsilon_i \sim N(0, 10^2)$, and x_i values are integers from 1 to 100. Plot the (x_i, y_i) -values, and estimate the parameters of that model.

```
> x <- 1:100
> y <- 5 + 0.1*x + rnorm(100,0,10)
> plot(x,y)
> abline(lm(y~x))
> summary(lm(y~x))$coef
```

Are your estimates consistent with the data-generating model? Run the code a couple of times to see the variability in the parameter estimates.

2.7 Analysis of hazard rates, their ratios and differences

This exercise is *very* prescriptive, so you should make an effort to really understand everything you type into R. Consult the relevant slides of the lecture on “Poisson regression for rates ...”

2.7.1 Hand calculations for a single rate

Let λ be the true **hazard rate** or theoretical incidence rate of a given outcome event. Its estimator is the empirical **incidence rate** $\hat{\lambda} = D/Y = \text{no. cases/person-years}$. Recall that the standard error of the empirical rate is $\text{SE}(\hat{\lambda}) = \hat{\lambda}/\sqrt{D}$.

The simplest approximate 95% confidence interval (CI) for λ is given by

$$\hat{\lambda} \pm 1.96 \times \text{SE}(\hat{\lambda})$$

An alternative approach is based on logarithmic transformation of the empirical rate. The standard error of the empirical log-rate $\hat{\theta} = \log(\hat{\lambda})$ is $\text{SE}(\hat{\theta}) = 1/\sqrt{D}$. Thus, a simple approximate 95% confidence interval for the log-hazard $\theta = \log(\lambda)$ is obtained from

$$\hat{\theta} \pm 1.96/\sqrt{D} = \log(\hat{\lambda}) \pm 1.96/\sqrt{D}$$

When taking the exponential from the above limits, we get another approximate confidence interval for the hazard λ itself:

$$\exp\{\log(\hat{\lambda}) \pm 1.96/\sqrt{D}\} = \hat{\lambda} \times \text{EF},$$

where $\text{EF} = \exp\{1.96 \times \text{SE}[\log(\hat{\lambda})]\}$ is the *error factor* associated with the 95% interval. This approach provides a more accurate approximation with small numbers of cases. (However, both these methods fail when $D = 0$, in which case an *exact* method or one based on *profile-likelihood* is needed.)

1. Suppose 15 outcome events are observed during 5532 person-years in a given study cohort. Let's use R as a simple desk calculator to estimate the underlying hazard rate λ (in 1000 person-years; therefore 5.532) and to get the first version of an approximate confidence interval:

```
> library( Epi )
> options(digits=4) # to cut down decimal points in the output

> D <- 15
> Y <- 5.532 # thousands of years!
> rate <- D / Y
> SE.rate <- rate/sqrt(D)
> c(rate, SE.rate, rate + c(-1.96, 1.96)*SE.rate )
[1] 2.7115 0.7001 1.3393 4.0837
```

2. Compute now the approximate confidence interval using the method based on log-transformation and compare the result with that in the previous item.

```
> SE.logr <- 1/sqrt(D)
> EF <- exp( 1.96 * SE.logr )
> c(log(rate), SE.logr)
[1] 0.9975 0.2582

> c( rate, EF, rate/EF, rate*EF )
[1] 2.711 1.659 1.635 4.498
```

2.7.2 Poisson model for a single rate with logarithmic link

You are able to estimate the hazard rate λ and compute its CI with a **Poisson regression model**, as described in the relevant slides in the lecture handout.

Poisson regression is a **generalized linear model** in which the **family**, *i.e.* the distribution of the response variable, is assumed to be the Poisson distribution. The most commonly applied **link function** in Poisson regression is the natural logarithm; log for short.

There are several ways of fitting a Poisson regression with these specifications in R.

3. The traditional way, described many textbooks and applied in most software, is based on using the number of events D as the response and the logarithm of person-years Y as an **offset** term.

– Fit now to the given data a simple Poisson model containing only the intercept term, save the results into a model object `m`, and print a summary of the results.

```
> m <- glm( D ~ 1, family=poisson(link=log), offset=log(Y) )
> summary( m )

Call:
glm(formula = D ~ 1, family = poisson(link = log), offset = log(Y))

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    0.998      0.258    3.86 0.00011 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for poisson family taken to be 1)

    Null deviance: 0  on 0  degrees of freedom
Residual deviance: 0  on 0  degrees of freedom
AIC: 6.557

Number of Fisher Scoring iterations: 3
```

Compare the figures below “Coefficients” to those you obtained from your hand calculations for `log(rate)` in section 1.6.2, item 2. – What did you get?

4. The summary method produces too much output for our purposes. You can extract CIs for the model parameters directly from the fitted model on the scale determined by the link function with function `ci.lin()`. Thus, the estimate, its SE, and confidence limits for the log-rate $\theta = \log(\lambda)$ are obtained by:

```
> ci.lin( m )

              Estimate StdErr      z      P    2.5% 97.5%
(Intercept)    0.9975 0.2582 3.863 0.0001119 0.4914 1.504
```

However, to get the point estimate and the confidence limits for the hazard rate $\lambda = \exp(\theta)$ itself on the original scale, the results must be exp-transformed:

```
> ci.lin( m, Exp=TRUE)
```

```

      Estimate StdErr      z      P exp(Est.)  2.5% 97.5%
(Intercept)  0.9975 0.2582 3.863 0.0001119    2.711 1.635 4.498

```

To get just the point estimate and CI for λ from log-transformed quantities you are recommended to use function `ci.exp()`, which is actually a wrapper of `ci.lin()`:

```

> ci.exp( m )

      exp(Est.)  2.5% 97.5%
(Intercept)    2.711 1.635 4.498

> ci.lin( m, Exp=TRUE)[, 5:7]

exp(Est.)      2.5%      97.5%
    2.711      1.635      4.498

```

Both functions are found from `Epi` package. – Note that the test statistic and P -value are rarely interesting quantities for a single rate.

- There is another method for fitting Poisson regression, which overcomes some of the limitations in the traditional method. A family object `poisreg`, a modified version of the original `poisson` family object, is available in package `Epi`. When using this, the response is defined as a *matrix* of two columns: numbers of cases D and person-years Y , these being combined into a matrix by `cbind(D,Y)`. No specification of `offset` is needed.

```

> mreg <- glm( cbind(D, Y) ~ 1, family=poisreg(link=log) )
> ci.exp( mreg )

      exp(Est.)  2.5% 97.5%
(Intercept)    2.711 1.635 4.498

```

In this course we endorse the use of family `poisreg` because of its advantages in more general settings.

2.7.3 Poisson model for a single rate with identity link

The approach leaning on having the number of cases D as the response and $\log(Y)$ as an offset, is limited only to models with log link. A major advantage of the `poisreg` family is that it allows a straightforward use of the *identity* link, too. With this link the response variable is the same, but the parameters to be directly estimated are now the rates itself and their differences, not the log-rates and their differences as with the log link.

- Fit a Poisson model with identity link to our simple data, and use `ci.lin()` to produce the estimate and the confidence interval for the hazard rate from this model:

```

> mid <- glm( cbind(D,Y) ~ 1, family=poisreg(link=identity) )
> ci.lin( mid )

      Estimate StdErr      z      P  2.5% 97.5%
(Intercept)    2.711 0.7001 3.873 0.0001075 1.339 4.084

> ci.lin( mid )[, c(1,5,6)]

```

Estimate	2.5%	97.5%
2.711	1.339	4.084

How is the coefficient of this model interpreted? Verify that you actually get the same rate estimate and CI as in section 1.6.1, item 1.

Comment. The confidence limits are not the same as from the multiplicative model, because they are derived from an approximation of the distribution of the *rate* being normally distributed, whereas the multiplicative model uses an assumption that the log-rate is normally distributed.

The confidence limits from this model are based on the 2nd derivative of the log-likelihood with respect to the *rate*, and not as before with respect to the *log rate*, and therefore they are different — they are symmetrical on the rate-scale and not on the log-rate scale:

$$\ell(\lambda) = D \ln(\lambda) - \lambda Y \quad \ell'(\lambda) = D/\lambda - Y \quad \ell''(\lambda) = -D/\lambda^2 \Big|_{\lambda=D/Y} = -Y^2/D$$

Thus the observed information is Y^2/D and hence the standard error of the incidence rate is square root of the inverse of this, \sqrt{D}/Y , which is exactly the standard error you got from the model:

```
> ci.lin( mid )

              Estimate StdErr      z      P  2.5% 97.5%
(Intercept)    2.711 0.7001 3.873 0.0001075 1.339 4.084

> sqrt(D)/Y

[1] 0.7001
```

2.7.4 Poisson model assuming the same rate for several periods

Now, suppose the events and person years are collected over three distinct periods.

7. Read in the data and compute period-specific rates

```
> Dx <- c(3,7,5)
> Yx <- c(1.412,2.783,1.337)
> Px <- 1:3
> rates <- Dx/Yx
> rates

[1] 2.125 2.515 3.740
```

8. Using these data, fit the same model with log link as in section 1.6.2, assuming a common single hazard λ for the separate periods. Compare the result from the previous ones

```
> m3 <- glm( cbind(Dx,Yx) ~ 1, family=poisreg(link=log) )
> ci.exp( m3 )
```

```

              exp(Est.)  2.5% 97.5%
(Intercept)    2.711 1.635 4.498

```

9. Now test whether the rates are the same in the three periods: Try to fit a model with the period as a factor in the model:

```

> mp <- glm( cbind(Dx,Yx) ~ factor(Px), family=poisreg(link=log) )
> ci.exp(mp)

              exp(Est.)  2.5% 97.5%
(Intercept)    2.125 0.6852 6.588
factor(Px)2    1.184 0.3061 4.578
factor(Px)3    1.760 0.4207 7.365

```

Compare the goodness-of-fit of the two models using function `anova()` with the argument `test="Chisq"`:

```

> anova( m3, mp, test="Chisq" )

Analysis of Deviance Table

Model 1: cbind(Dx, Yx) ~ 1
Model 2: cbind(Dx, Yx) ~ factor(Px)
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1         2         0.7              0.7
2         0         0.0  2         0.7      0.7

```

Compare the test statistic to the deviance of the model `mp`. – What is the deviance indicating?

Comment. We see that the deviance of the model with the constant rate is the same as the likelihood-ratio test statistic of that model against the “bigger” model with three separate rates. The deviance statistic is namely in general the likelihood-ratio test of a given model, considered as a “null hypothesis”, versus the saturated, *i.e.* most detailed model possible for the dataset. And in this case, with a dataset of 3 observations, the most detailed model is exactly the one we fitted with a separate rate for each line of observation in the dataset.

2.7.5 Analysis of rate ratio

We now switch to comparison of two rates λ_1 and λ_0 , *i.e.* the hazard in an exposed group vs. that in an unexposed one.

Consider first estimation of the **hazard ratio** or the underlying “true” rate ratio $\rho = \lambda_1/\lambda_0$ between the groups. Suppose we have pertinent empirical data (cases and person-times) from both groups, (D_1, Y_1) and (D_0, Y_0) . The point estimate of ρ is the empirical **incidence rate ratio**

$$\hat{\rho} = \text{RR} = \frac{\hat{\lambda}_1}{\hat{\lambda}_0} = \frac{D_1/Y_1}{D_0/Y_0}$$

The variance of $\log(\text{RR})$, that is, the difference of the log of the empirical rates, $\log(\hat{\lambda}_1) - \log(\hat{\lambda}_0)$, is commonly estimated as

$$\begin{aligned} \text{var}(\log(\text{RR})) &= \text{var}\{\log(\hat{\lambda}_1/\hat{\lambda}_0)\} = \text{var}\{\log(\hat{\lambda}_1)\} + \text{var}\{\log(\hat{\lambda}_0)\} \\ &= 1/D_1 + 1/D_0 \end{aligned}$$

Based on a similar argument as before, an approximate 95% CI for the true rate ratio λ_1/λ_0 is then:

$$RR \div \exp \left(1.96 \sqrt{\frac{1}{D_1} + \frac{1}{D_0}} \right)$$

Suppose you have 15 events during 5532 person-years in an unexposed group and 28 events during 4783 person-years in an exposed group:

10. Calculate the incidence rates in the two groups, their ratio, and the CI of the true hazard ratio ρ by direct application of the above formulae:

```
> D0 <- 15 ; D1 <- 28
> Y0 <- 5.532 ; Y1 <- 4.783
> R1 <- D1/Y1; R0 <- D0/Y0
> RR <- R1/R0
> SE.lrr <- sqrt(1/D0+1/D1)
> EF <- exp( 1.96 * SE.lrr)
> c( R1, R0, RR, RR/EF, RR*EF )
[1] 5.854 2.711 2.159 1.153 4.042
```

11. Now achieve this using a Poisson model. For that we first combine the group-specific numbers into pertinent vectors and specify a factor to represent the contrast between the exposed and the unexposed group

```
> D <- c(D0,D1) ; Y <- c(Y0,Y1); expos <- 0:1
> mm <- glm( cbind(D,Y) ~ factor(expos), family=poisreg(link=log) )
```

What do the parameters mean in this model?

12. You can extract the estimation results for exponentiated parameters in two ways, as before:

```
> ci.exp( mm )

              exp(Est.)  2.5% 97.5%
(Intercept)      2.711 1.635 4.498
factor(expos)1    2.159 1.153 4.042

> ci.lin( mm, Exp=TRUE ) [,5:7]

              exp(Est.)  2.5% 97.5%
(Intercept)      2.711 1.635 4.498
factor(expos)1    2.159 1.153 4.042
```

2.7.6 Analysis of rate difference

For the **hazard difference** $\delta = \lambda_1 - \lambda_0$, the natural estimator is the **incidence rate difference**

$$\hat{\delta} = \hat{\lambda}_1 - \hat{\lambda}_0 = D_1/Y_1 - D_0/Y_0 = RD.$$

Its variance is just the sum of the variances of the two rates

$$\begin{aligned} \text{var}(RD) &= \text{var}(\hat{\lambda}_1) + \text{var}(\hat{\lambda}_0) \\ &= D_1/Y_1^2 + D_0/Y_0^2 \end{aligned}$$

13. Use this formula to compute the point estimate of the rate difference λ and a 95% confidence interval for it:

```
> RD <- diff( D/Y )      ## or RD <- R1 - R0
> SED <- sqrt( sum( D/Y^2 ) )
> c( R1, R0, RD, SED, RD+c(-1,1)*1.96*SED )
[1] 5.8541 2.7115 3.1426 1.3092 0.5765 5.7087
```

14. Verify that this is the confidence interval you get when you fit an additive model (obtained by identity link) with exposure as a factor:

```
> ma <- glm( cbind(D,Y) ~ factor(expos),
+           family=poisreg(link=identity) )
> ci.lin( ma )[, c(1,5,6)]
```

	Estimate	2.5%	97.5%
(Intercept)	2.711	1.3393	4.084
factor(expos)1	3.143	0.5765	5.709

2.7.7 Optional/Homework: Identity link with weighting

Do this only after you have done the other exercises of this session, i.e. those in section 1.7.

15. There is yet another way of fitting Poisson regression models in R. It is based on using the original family `poisson` but having the empirical rate $\hat{\lambda} = D/Y$ as a **scaled** Poisson response, and the person-years Y as a **weight** variable instead of an offset term. – When applying this procedure, it will give you a warning about a non-integer response in a Poisson model, but you can ignore this warning

```
> mwei <- glm( D/Y ~ 1, family=poisson(link=log), weight=Y )
> ci.exp( mwei )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	4.169	3.092	5.621

Verify that this gave the same results as above.

16. Repeat the model fitting parts in sections 1.6.5, and 1.6.6. using this approach based on weighting, in which the response is D/Y , the family is `poisson`, and `weight = Y`. Verify that you got similar results.

2.7.8 Optional/Homework: Calculations using matrix tools

NB. This subsection requires some familiarity with matrix algebra. Do this only after you have done the other exercises of this session.

17. Explore the function `ci.mat()`, which lets you use matrix multiplication (operator `'%*%'` in R) to produce a confidence interval from an estimate and its standard error (or CIs from whole columns of estimates and SEs):

```

> ci.mat
function (alpha = 0.05, df = Inf)
{
  ciM <- rbind(c(1, 1, 1), qt(1 - alpha/2, df) * c(0, -1, 1))
  colnames(ciM) <- c("Estimate", paste(formatC(100 * alpha/2,
    format = "f", digits = 1), "%", sep = ""), paste(formatC(100 *
    (1 - alpha/2), format = "f", digits = 1), "%", sep = ""))
  ciM
}
<bytecode: 0x561461dfe530>
<environment: namespace:Epi>

> ci.mat()

      Estimate  2.5% 97.5%
[1,]         1  1.00  1.00
[2,]         0 -1.96  1.96

```

As you see, this function returns a 2×3 matrix (2 rows, 3 columns) containing familiar numbers.

18. When you combine the single rate and its standard error into a row vector of length 2, i.e. a 1×2 matrix, and multiply this by the 2×3 matrix above, the computation returns a 1×3 matrix containing the point estimate and the confidence limit. – Apply this method to the single rate calculations in 1.6.1; first creating the 1×2 matrix and then performing the matrix multiplication.

```

> rateandSE <- c( rate, SE.rate )
> rateandSE

[1] 2.7115 0.7001

> rateandSE %*% ci.mat()

      Estimate  2.5% 97.5%
[1,]    2.711 1.339 4.084

```

19. When the confidence interval is based on the log-rate and its standard error, the result is obtained by appropriate application of the exp-function on the pertinent matrix product

```

> lograndSE <- c( log(rate), SE.logr )
> lograndSE

[1] 0.9975 0.2582

> exp( lograndSE %*% ci.mat() )

      Estimate  2.5% 97.5%
[1,]    2.711 1.635 4.498

```

20. For computing the rate ratio and its CI as in 1.6.5, matrix multiplication with `ci.mat()` should give the same result as there:

```

> exp( c( log(RR), SE.lrr ) %*% ci.mat() )

```

```

      Estimate  2.5% 97.5%
[1,]      2.159 1.153 4.042

```

21. The main argument in function `ci.mat()` is `alpha`, which sets the confidence level: $1 - \alpha$. The default value is `alpha = 0.05`, corresponding to the level $1 - 0.05 = 95\%$. If you wish to get the confidence interval for the rate ratio at the 90 % level ($= 1 - 0.1$), for instance, you may proceed as follows:

```

> ci.mat( alpha=0.1 )

      Estimate   5.0% 95.0%
[1,]          1  1.000 1.000
[2,]          0 -1.645 1.645

> exp( c( log(RR), SE.lrr ) %*% ci.mat(alpha=0.1) )

      Estimate   5.0% 95.0%
[1,]      2.159 1.275 3.654

```

22. Look again to the model used to analyse the rate ratio in 2.7.5. Often one would like to get simultaneously both the rates and the ratio between them. This can be achieved in one go using the *contrast matrix* argument `ctr.mat` to `ci.lin()` or `ci.exp()`. Try:

```

> CM <- rbind( c(1,0), c(1,1), c(0,1) )
> rownames( CM ) <- c("rate 0", "rate 1", "RR 1 vs. 0")
> CM

      [,1] [,2]
rate 0      1      0
rate 1      1      1
RR 1 vs. 0    0      1

> mm <- glm( D ~ factor(expos),
+           family=poisson(link=log), offset=log(Y) )
> ci.exp( mm, ctr.mat=CM )

      exp(Est.)  2.5% 97.5%
rate 0      2.711 1.635 4.498
rate 1      5.854 4.042 8.479
RR 1 vs. 0    2.159 1.153 4.042

```

23. Use the same machinery to the additive model to get the rates and the rate-difference in one go. Note that the annotation of the resulting estimates are via the column-names of the contrast matrix.

```

> rownames( CM ) <- c("rate 0", "rate 1", "RD 1 vs. 0")
> ma <- glm( cbind(D,Y) ~ factor(expos),
+           family=poisreg(link=identity) )
> ci.lin( ma, ctr.mat=CM )[ , c(1,5,6)]

      Estimate  2.5% 97.5%
rate 0      2.711 1.3393 4.084
rate 1      5.854 3.6857 8.022
RD 1 vs. 0    3.143 0.5765 5.709

```

2.8 Logistic regression (GLM)

2.8.1 Malignant melanoma in Denmark

In the mid-80s a case-control study on risk factors for malignant melanoma was conducted in Denmark (Østerlind et al. The Danish case-control study of cutaneous malignant melanoma I: Importance of host factors. *Int J Cancer* 1988; 42: 200-206).

The cases were patients with skin melanoma (excluding lentigo melanoma), newly diagnosed from 1 Oct, 1982 to 31 March, 1985, aged 20-79, from East Denmark, and they were identified from the Danish Cancer Registry.

The controls (twice as many as cases) were drawn from the residents of East Denmark in April, 1984, as a random sample stratified by sex and age (within the same 5 year age group) to reflect the sex and age distribution of the cases. This is called group matching, and in such a study, it is necessary to control for age and sex in the statistical analysis. (Yes indeed: In spite of the fact that stratified sampling by sex and age removed the statistical association of these variables with melanoma from the final case-control data set, the analysis must control for variables which determine the probability of selecting subjects from the base population to the study sample.)

The population of East Denmark is a dynamic one. Sampling the controls only at one time point is a rough approximation of *incidence density sampling*, which ideally would spread out over the whole study period. Hence the exposure odds ratios calculable from the data are estimates of the corresponding hazard rate ratios between the exposure groups.

After exclusions, refusals etc., 474 cases (92% of eligible cases) and 926 controls (82%) were interviewed. This was done face-to-face with a structured questionnaire by trained interviewers, who were not informed about the subject's case-control status.

For this exercise we have selected a few host variables from the study in an ascii-file, `melanoma.dat`. The variables are listed in table 2.1.

Table 2.1: *Variables in the melanoma dataset.*

Variable	Units or Coding	Type	Name
Case-control status	1=case, 0=control	numeric	<code>cc</code>
Sex	1=male, 2=female	numeric	<code>sex</code>
Age at interview	age in years	numeric	<code>age</code>
Skin complexion	0=dark, 1=medium, 2=light	numeric	<code>skin</code>
Hair colour	0=dark brown/black, 1=light brown, 2=blonde, 3=red	numeric	<code>hair</code>
eye colour	0=brown, 1=grey, green, 2=blue	numeric	<code>eyes</code>
Freckles	1=many, 2=some, 3=none	numeric	<code>freckles</code>
Naevi, small	no. naevi < 5mm	numeric	<code>nvsmall</code>
Naevi, largs	no. naevi ≥ 5mm	numeric	<code>nvlarge</code>

2.8.2 Reading the data

Start R and load the `Epi` package using the function `library()`. Read the data set from the file `melanoma.dat` found in the course website to a data frame with name `mel` using the `read.table()` function. Remember to specify that missing values are coded ".", and that variable names are in the first line of the file. View the overall structure of the data frame, and list the first 20 rows of `mel`.

```
> library(Epi)
> mel <- read.table("http://bendixcarstensen.com/SPE/data/melanoma.dat", header=TRUE, na.string=".", as.is=TRUE)
> str(mel)
```

```
'data.frame':      1400 obs. of  9 variables:
 $ cc      : int  1 1 1 0 1 0 0 0 0 1 ...
 $ sex     : int  2 1 2 2 2 2 2 1 2 2 ...
 $ age     : int  71 68 42 66 36 68 68 39 75 49 ...
 $ skin    : int  2 2 1 0 1 2 0 2 2 2 ...
 $ hair    : int  0 0 1 2 0 2 0 0 0 1 ...
 $ eyes    : int  2 2 2 1 2 2 1 2 2 2 ...
 $ freckles: int  2 1 3 2 3 2 2 2 1 2 ...
 $ nvsmall : int  2 3 22 0 1 0 0 3 5 6 ...
 $ nvlarge : int  0 0 1 0 0 0 0 0 0 0 ...
```

```
> head(mel, n=20)
```

	cc	sex	age	skin	hair	eyes	freckles	nvsmall	nvlarge
1	1	2	71	2	0	2	2	2	0
2	1	1	68	2	0	2	1	3	0
3	1	2	42	1	1	2	3	22	1
4	0	2	66	0	2	1	2	0	0
5	1	2	36	1	0	2	3	1	0
6	0	2	68	2	2	2	2	0	0
7	0	2	68	0	0	1	2	0	0
8	0	1	39	2	0	2	2	3	0
9	0	2	75	2	0	2	1	5	0
10	1	2	49	2	1	2	2	6	0
11	0	1	48	2	1	2	3	4	0
12	1	2	67	0	0	2	2	1	0
13	0	1	50	1	0	2	3	4	0
14	1	2	38	2	0	1	3	8	0
15	0	2	33	2	1	2	2	3	0
16	0	2	39	1	0	1	3	0	2
17	0	2	39	1	1	2	3	0	0
18	1	1	50	0	1	1	1	3	1
19	0	2	35	2	0	2	2	1	0
20	0	2	35	2	0	1	3	5	0

2.8.3 House keeping

The structure of the data frame `mel` tells us that all the variables are numeric (integer), so first you need to do a bit of house keeping. For example the variables `sex`, `skin`, `hair`, `eye` need to be converted to factors, with labels, and `freckles` which is coded 4 for none down to 1 for many (not very intuitive) needs to be recoded, and relabelled.

To avoid too much typing and to leave plenty of time to think about the analysis, these house keeping commands are in a script file called `melanoma-house.r`. You should study this script carefully before running it. The coding of `freckles` can be reversed by subtracting the

current codes from 4. Once recoded the variable needs to be converted to a factor with labels "none", etc. Age is currently a numeric variable recording age to the nearest year, and it will be convenient to group these values into (say) 10 year age groups, using `cut`. In this case we choose to create a new variable, rather than change the original.

```
> source("http://bendixcarstensen.com/SPE/data/melanoma-house.r")
```

Look again at the structure of the data frame `mel` and note the changes. Use the command `summary(mel)` to look at the univariate distributions.

```
> str(mel)
'data.frame':      1400 obs. of  13 variables:
 $ cc      : int   1 1 1 0 1 0 0 0 1 ...
 $ sex     : Factor w/ 2 levels "M","F": 2 1 2 2 2 2 1 2 2 ...
 $ age     : int   71 68 42 66 36 68 68 39 75 49 ...
 $ skin    : Factor w/ 3 levels "dark","medium",...: 3 3 2 1 2 3 1 3 3 3 ...
 $ hair    : Factor w/ 4 levels "dark","light_brown",...: 1 1 2 3 1 3 1 1 1 2 ...
 $ eyes    : Factor w/ 3 levels "brown","grey-green",...: 3 3 3 2 3 3 2 3 3 3 ...
 $ freckles: Factor w/ 3 levels "none","some",...: 2 3 1 2 1 2 2 2 3 2 ...
 $ nvsmall : int   2 3 22 0 1 0 0 3 5 6 ...
 $ nvlarge : int   0 0 1 0 0 0 0 0 0 0 ...
 $ age.cat : Factor w/ 6 levels "[20,30)","[30,40)",...: 6 5 3 5 2 5 5 2 6 3 ...
 $ hair2   : Factor w/ 2 levels "dark","other": 1 1 2 2 1 2 1 1 1 2 ...
 $ nvsm4   : Factor w/ 4 levels "[0,1)","[1,2)",...: 3 3 4 1 2 1 1 3 4 4 ...
 $ nvlar3  : Factor w/ 3 levels "[0,1)","[1,2)",...: 1 1 2 1 1 1 1 1 1 1 ...

> summary(mel)

      cc      sex      age      skin      hair
Min.   :0.0000  M:584  Min.   :21.00  dark   :318  dark    :690
1st Qu.:0.0000  F:816  1st Qu.:42.00  medium:594  light_brown:548
Median :0.0000           Median :53.00  light  :478  blonde   : 61
Mean   :0.3386           Mean   :52.89  NA's   : 10  red     :101
3rd Qu.:1.0000           3rd Qu.:64.00
Max.   :1.0000           Max.   :81.00

      eyes      freckles      nvsmall      nvlarge      age.cat
brown      :187  none:633  Min.      : 0.000  Min.      : 0.0000  [20,30): 61
grey-green:450  some:526  1st Qu.: 0.000  1st Qu.: 0.0000  [30,40):202
blue       :757  many:237  Median : 0.000  Median : 0.0000  [40,50):347
NA's       : 6   NA's: 4   Mean      : 1.163  Mean      : 0.1565  [50,60):296
              3rd Qu.: 1.000  3rd Qu.: 0.0000  [60,70):307
              Max.      :46.000  Max.      :14.0000  [70,85):187
              NA's      :7      NA's      :7

      hair2      nvsm4      nvlar3
dark :690  [0,1) :922  [0,1) :1263
other:710  [1,2) :192  [1,2) : 95
          [2,5) :176  [2,15): 35
          [5,50):103  NA's : 7
          NA's : 7
```

This is enough housekeeping for now - let's turn to something a bit more interesting.

2.8.4 One variable at a time

As a first step it is a good idea to start by looking at the numbers of cases and controls by each variable separately, ignoring age and sex. Try

```
> with(mel, table(cc,skin))
      skin
cc dark medium light
0  232    391   296
1   86    203   182

> stat.table(skin, contents=ratio(cc,1-cc), data=mel)

-----
skin      ratio(cc,
                1 - cc)
-----
dark              0.37
medium            0.52
light             0.61
-----
```

to see the numbers of cases and controls, as well as the odds of being a case by skin colour

Now use `effx()` to get crude estimates of the hazard ratios for the effect of skin colour.

```
> effx(cc, type="binary", exposure=skin, data=mel)

-----
response      : cc
type          : binary
exposure      : skin

skin is a factor with levels: dark / medium / light
baseline is dark
effects are measured as odds ratios
-----

effect of skin on cc
number of observations 1390

              Effect 2.5% 97.5%
medium vs dark   1.40 1.04  1.89
light vs dark    1.66 1.22  2.26

Test for no effects of exposure on 2 df: p-value= 0.00499
```

- Look at the crude effect estimates of hair, eyes and freckles in the same way.

```
> with(mel, table(cc,hair))
      hair
cc dark light_brown blonde red
0  490        341     36  59
1  200        207     25  42

> stat.table(hair, contents=ratio(cc,1-cc), data=mel)

-----
hair      ratio(cc,
                1 - cc)
-----
dark              0.41
light_brown       0.61
blonde            0.69
red               0.71
-----
```



```
> effx(cc,type="binary",exposure=hair,data=mel)
```

```
-----
response      : cc
type          : binary
exposure      : hair
```

```
hair is a factor with levels: dark / light_brown / blonde / red
baseline is dark
effects are measured as odds ratios
-----
```

```
effect of hair on cc
number of observations 1400
```

	Effect	2.5%	97.5%
light_brown vs dark	1.49	1.170	1.89
blonde vs dark	1.70	0.995	2.91
red vs dark	1.74	1.140	2.68

```
Test for no effects of exposure on 3 df: p-value= 0.0017
```

```
> with(mel, table(cc,eyes))
```

```
      eyes
cc  brown grey-green blue
0   123      312  488
1    64      138  269
```

```
> stat.table(eyes, contents=ratio(cc,1-cc), data=mel)
```

```
-----
eyes      ratio(cc,
                1 - cc)
-----
brown      0.52
grey-green 0.44
blue       0.55
-----
```

```
> effx(cc, type="binary", exposure=eyes, data=mel)
```

```
-----
response      : cc
type          : binary
exposure      : eyes
```

```
eyes is a factor with levels: brown / grey-green / blue
baseline is brown
effects are measured as odds ratios
-----
```

```
effect of eyes on cc
number of observations 1394
```

	Effect	2.5%	97.5%
grey-green vs brown	0.85	0.592	1.22
blue vs brown	1.06	0.756	1.48

```
Test for no effects of exposure on 2 df: p-value= 0.22
```

```
> with(mel, table(cc,freckles))
```

```

      freckles
cc none some many
  0  466  343  114
  1  167  183  123
> stat.table(freckles, contents=ratio(cc,1-cc),data=mel)

-----
freckles    ratio(cc,
                1 - cc)
-----
none                0.36
some                0.53
many                1.08
-----

> effx(cc, type="binary", exposure=freckles, data=mel)

-----
response      : cc
type          : binary
exposure      : freckles

freckles is a factor with levels: none / some / many
baseline is none
effects are measured as odds ratios
-----

effect of freckles on cc
number of observations 1396

              Effect 2.5% 97.5%
some vs none    1.49 1.16  1.92
many vs none    3.01 2.21  4.11

Test for no effects of exposure on 2 df: p-value= 2.15e-11

```

2.8.5 Generalized linear models with binomial family and logit link

The function `effx()` is just a wrapper for the `glm()` function, and you can show this by fitting the glm directly with

```

> mf <- glm(cc ~ freckles, family="binomial", data=mel)
> round(ci.exp( mf ),2)

              exp(Est.) 2.5% 97.5%
(Intercept)    0.36 0.30  0.43
frecklessome    1.49 1.16  1.92
frecklesmany    3.01 2.21  4.11
>

```

Comparison with the output from `effx()` shows the results to be the same.

Note that in `effx()` the type of response is “binary” whereas in `glm()` the family of probability distributions used to fit the model is “binomial”. There is a 1-1 relationship between type of response and family:

metric	gaussian
binary	binomial
failure/count	poisson

2.8.6 Controlling for age and sex

Because the probability that a control is selected into the study depends on age and sex it is necessary to control for age and sex. For example, the effect of freckles controlled for age and sex is obtained with

```
> effx(cc, typ="binary", exposure=freckles, control=list(age.cat,sex),data=mel)
```

```
-----
response      : cc
type          : binary
exposure      : freckles
control vars  : age.cat sex
```

```
freckles is a factor with levels: none / some / many
baseline is none
effects are measured as odds ratios
-----
```

```
effect of freckles on cc
controlled for age.cat sex
```

```
number of observations 1396
```

	Effect	2.5%	97.5%
some vs none	1.51	1.17	1.95
many vs none	3.07	2.24	4.22

```
Test for no effects of exposure on 2 df: p-value= 2.55e-11
```

or

```
> mfas <- glm(cc ~ freckles + age.cat + sex, family="binomial", data=mel)
> round(ci.exp(mfas), 2)
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.41	0.23	0.72
frecklessome	1.51	1.17	1.95
frecklesmany	3.07	2.24	4.22
age.cat[30,40)	0.90	0.49	1.67
age.cat[40,50)	0.91	0.51	1.62
age.cat[50,60)	0.97	0.54	1.75
age.cat[60,70)	0.82	0.45	1.48
age.cat[70,85)	0.89	0.48	1.65
sexF	0.94	0.74	1.19

Do the adjusted estimates differ from the crude ones that you computed with `effx()`?

2.8.7 Likelihood ratio tests

There are 2 effects estimated for the 3 levels of `freckles`, and `glm()` provides a test for each effect separately, but to test for no effect at all of `freckles` you need a likelihood ratio test. This involves fitting two models, one without `freckles` and one with, and recording the change in deviance. Because there are some missing values for `freckles` it is necessary to restrict the first model to those subjects who have values for `freckles`.

```
> mas <- glm(cc ~ age.cat + sex, family="binomial", data=subset(mel, !is.na(freckles)))
> anova(mas, mfas, test="Chisq")
```

Analysis of Deviance Table

```

Model 1: cc ~ age.cat + sex
Model 2: cc ~ freckles + age.cat + sex
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1      1389      1785.9
2      1387      1737.1  2    48.786 2.549e-11 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

The change in residual deviance is $1785.9 - 1737.1 = 48.8$ on $1389 - 1387 = 2$ degrees of freedom. The P -value corresponding to this change is obtained from the upper tail of the cumulative distribution of the χ^2 -distribution with 2 df:

```

> 1 - pchisq(48.786, 2)
[1] 2.548328e-11

```

- There are 3 effects for the 4 levels of hair colour (**hair**). To obtain adjusted estimates for the effect of hair colour and to test the pertinent null hypothesis fit the relevant models, print the and use `anova` to test for no effects of hair colour.

```

              exp(Est.) 2.5% 97.5%
(Intercept)      0.39 0.22  0.69
hairlight_brown  1.50 1.18  1.91
hairblonde       1.68 0.98  2.88
hairred          1.78 1.16  2.75
age.cat[30,40)   0.98 0.53  1.79
age.cat[40,50)   0.98 0.55  1.75
age.cat[50,60)   1.17 0.65  2.11
age.cat[60,70)   0.98 0.55  1.77
age.cat[70,85)   1.13 0.61  2.08
sexF             1.00 0.79  1.26

```

Analysis of Deviance Table

```

Model 1: cc ~ age.cat + sex
Model 2: cc ~ hair + age.cat + sex
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1      1393      1790.7
2      1390      1775.2  3    15.434 0.001481 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

Compare the estimates with the crude ones and assess the evidence against the null hypothesis.

2.8.8 Relevelling

From the above you can see that subjects at each of the 3 levels light-brown, blonde, and red, are at greater risk than subjects with dark hair, with similar odds ratios. This suggests creating a new variable **hair2** which has just two levels, dark and the other three. The `Relevel()` function in `Epi` has been used for this in the house keeping script.

- Use `effx()` to compute the odds-ratio of melanoma between persons with red, blonde or light brown hair versus those with dark hair.

```
> effx(cc, type="binary", exposure=hair2, control=list(age.cat,sex), data=mel)
```

```
-----
response      : cc
type          : binary
exposure      : hair2
control vars   : age.cat sex
```

```
hair2 is a factor with levels: dark / other
baseline is dark
effects are measured as odds ratios
-----
```

```
effect of hair2 on cc
controlled for age.cat sex
```

```
number of observations 1400
```

```
Effect    2.5%  97.5%
      1.55   1.24   1.95
```

```
Test for no effects of exposure on 1 df: p-value= 0.000124
```

Reproduce these results by fitting an appropriate glm.

```
> mh2 <- glm(cc ~ hair2 + age.cat + sex, family="binomial",
+           data = subset(mel, !is.na(hair2)) )
> ci.exp(mh2 )
```

```
exp(Est.)      2.5%      97.5%
(Intercept)    0.3894010 0.2199868 0.6892829
hair2other      1.5541887 1.2396159 1.9485894
age.cat[30,40)  0.9740838 0.5302331 1.7894756
age.cat[40,50)  0.9872390 0.5539667 1.7593852
age.cat[50,60)  1.1722458 0.6529651 2.1044926
age.cat[60,70)  0.9847738 0.5491367 1.7660074
age.cat[70,85)  1.1277140 0.6121944 2.0773447
sexF            1.0034944 0.7978073 1.2622108
```

Use also a likelihood ratio test to test for the effect of `hair2`.

```
> m1 <- glm(cc ~ age.cat + sex, data = subset(mel, !is.na(hair2)) )
> anova(m1, mh2, test="Chisq")
```

Analysis of Deviance Table

```
Model 1: cc ~ age.cat + sex
Model 2: cc ~ hair2 + age.cat + sex
  Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1      1393      313.17
2      1392      1775.93  1  -1462.8
```

2.8.9 Controlling for other variables

When you control the effect of an exposure for some variable you are asking a question about what would the effect be if the variable is kept constant. For example, consider the effect of `freckles` controlled for `hair2`. We first stratify by `hair2` with

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex), strata=hair2, data=mel)
```

```
-----
response      : cc
type          : binary
exposure       : freckles
control vars   : age.cat sex
stratified by  : hair2
```

```
freckles is a factor with levels: none / some / many
baseline is none
hair2 is a factor with levels: dark/other
effects are measured as odds ratios
-----
```

```
effect of freckles on cc
controlled for age.cat sex
```

```
stratified by hair2
```

```
number of observations 1396
```

	Effect	2.5%	97.5%
strata dark level some vs none	1.61	1.11	2.34
strata other level some vs none	1.42	1.00	2.01
strata dark level many vs none	2.84	1.76	4.58
strata other level many vs none	3.15	2.06	4.80

```
Test for effect modification on 2 df: p-value= 0.757
```

The effect of freckles is still apparent in each of the two strata for hair colour. Use `effx()` to control for `hair2`, too, in addition to `age.cat` and `sex`.

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex,hair2), data=mel)
```

```
-----
response      : cc
type          : binary
exposure       : freckles
control vars   : age.cat sex hair2
```

```
freckles is a factor with levels: none / some / many
baseline is none
effects are measured as odds ratios
-----
```

```
effect of freckles on cc
controlled for age.cat sex hair2
```

```
number of observations 1396
```

	Effect	2.5%	97.5%
some vs none	1.51	1.17	1.95
many vs none	3.02	2.19	4.15

```
Test for no effects of exposure on 2 df: p-value= 6.9e-11
```

It is tempting to control for variables without thinking about the question you are thereby asking. This can lead to nonsense.

2.8.10 Stratification using glm()

We shall reproduce the output from

```
> effx(cc, type="binary", exposure=freckles,
+       control=list(age.cat,sex), strata=hair2,data=mel)
```

```
response      : cc
type          : binary
exposure      : freckles
control vars  : age.cat sex
stratified by : hair2

freckles is a factor with levels: none / some / many
baseline is none
hair2 is a factor with levels: dark/other
effects are measured as odds ratios
```

```
effect of freckles on cc
controlled for age.cat sex

stratified by hair2

number of observations 1396
```

	Effect	2.5%	97.5%
strata dark level some vs none	1.61	1.11	2.34
strata other level some vs none	1.42	1.00	2.01
strata dark level many vs none	2.84	1.76	4.58
strata other level many vs none	3.15	2.06	4.80

```
Test for effect modification on 2 df: p-value= 0.757

using glm(). To do this requires a nested model formula:
> mfas.h <- glm(cc ~ hair2/freckles + age.cat + sex, family="binomial", data=mel)
> ci.exp(mfas.h )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.3169581	0.1725855	0.5821023
hair2other	1.5639083	1.0920425	2.2396650
age.cat[30,40)	0.9286674	0.5004220	1.7233920
age.cat[40,50)	0.9573093	0.5328744	1.7198068
age.cat[50,60)	1.0464308	0.5776057	1.8957872
age.cat[60,70)	0.8495081	0.4692660	1.5378570
age.cat[70,85)	0.9351315	0.5020370	1.7418455
sexF	0.9012339	0.7114142	1.1417014
hair2dark:frecklessome	1.6123583	1.1106965	2.3406026
hair2other:frecklessome	1.4196216	1.0015163	2.0122743
hair2dark:frecklesmany	2.8378600	1.7567458	4.5842996
hair2other:frecklesmany	3.1469251	2.0628414	4.8007266

In amongst all the other effects you can see the two effects of freckles for dark hair (1.61 and 2.84) and the two effects of freckles for other hair (1.42 and 3.15).

2.8.11 Naevi

The distributions of `nvsmall` and `nvlarge` are very skew to the right. You can see this with

- ```
> stat.table(list(nvsma4,nvlar3),contents=percent(nvlar3),data=mel)
```



```

-----nvlar3-----
nvsm4 [0,1) [1,2) [2,15)

[0,1) 93.9 4.9 1.2
[1,2) 89.6 8.3 2.1
[2,5) 85.8 9.7 4.5
[5,50) 71.8 16.5 11.7

```

> #High frequencies on the diagonal shows a strong association

- Compute the sex- and age-adjusted OR estimates (with 95% CIs) associated with the number of small naevi first by using `effx()`, and then by fitting separate glms including `sex`, `age.cat` and `nvsm4` in the model formula.

```
> effx(cc,type="binary",exposure=nvsm4,control=list(age.cat,sex),data=mel)
```

```

response : cc
type : binary
exposure : nvsm4
control vars : age.cat sex

```

```

nvsm4 is a factor with levels: [0,1) / [1,2) / [2,5) / [5,50)
baseline is [0,1)
effects are measured as odds ratios

```

```

effect of nvsm4 on cc
controlled for age.cat sex

```

```
number of observations 1393
```

```

 Effect 2.5% 97.5%
[1,2) vs [0,1) 1.59 1.15 2.21
[2,5) vs [0,1) 2.47 1.77 3.43
[5,50) vs [0,1) 5.06 3.28 7.81

```

```
Test for no effects of exposure on 3 df: p-value= <2e-16
```

```
> mns <- glm(cc ~ nvsm4 + age.cat + sex, family="binomial",data=mel)
> round(ci.exp(mns), 2)
```

```

 exp(Est.) 2.5% 97.5%
(Intercept) 0.36 0.20 0.64
nvsm4[1,2) 1.59 1.15 2.21
nvsm4[2,5) 2.47 1.77 3.43
nvsm4[5,50) 5.06 3.28 7.81
age.cat[30,40) 0.96 0.51 1.80
age.cat[40,50) 1.02 0.56 1.85
age.cat[50,60) 1.16 0.64 2.13
age.cat[60,70) 1.07 0.58 1.96
age.cat[70,85) 1.17 0.62 2.21
sexF 0.96 0.76 1.21

```

- Do the same with large naevi `nvlar3`.

```
> effx(cc, type="binary", exposure=nvlar3, control=list(age.cat,sex), data=mel)
```

```

response : cc
type : binary
exposure : nvlar3
control vars : age.cat sex

nvlar3 is a factor with levels: [0,1) / [1,2) / [2,15)
baseline is [0,1)
effects are measured as odds ratios

effect of nvlar3 on cc
controlled for age.cat sex

number of observations 1393

 Effect 2.5% 97.5%
[1,2) vs [0,1) 1.82 1.19 2.78
[2,15) vs [0,1) 3.58 1.78 7.21

Test for no effects of exposure on 2 df: p-value= 4.81e-05
> mnl <- glm(cc ~ nvlar3 + age.cat + sex, family="binomial", data=mel)
> round(ci.exp(mnl), 2)

 exp(Est.) 2.5% 97.5%
(Intercept) 0.49 0.28 0.85
nvlar3[1,2) 1.82 1.19 2.78
nvlar3[2,15) 3.58 1.78 7.21
age.cat[30,40) 0.90 0.49 1.66
age.cat[40,50) 0.92 0.52 1.63
age.cat[50,60) 1.07 0.60 1.91
age.cat[60,70) 0.89 0.50 1.60
age.cat[70,85) 1.00 0.54 1.84
sexF 1.03 0.82 1.29

```

• Now fit a glm containing `age.cat`, `sex`, `nvsma4` and `nvlar3`. What is the interpretation of the coefficients for `nvsma4` and `nvlar3`?

```

> mnls <- glm(cc ~ nvsma4 + nvlar3 + age.cat + sex, family="binomial", data=mel)
> # Coeffs for nvsma4 are the effects of nvsma4 controlled for age.cat, sex, and nvlar3.
> # Similarly for the coefficients for nvlar3.

```

### 2.8.12 Treating freckles as a numeric exposure

The evidence for the effect of `freckles` is already convincing. However, to demonstrate how it is done, we shall perform a linear trend test by treating freckles as a numeric exposure.

```

> mel$fscore<-as.numeric(mel$freckles)
> effx(cc, type="binary", exposure=fscore, control=list(age.cat,sex), data=mel)

response : cc
type : binary
exposure : fscore
control vars : age.cat sex

fscore is numeric

```

effects are measured as odds ratios

-----

effect of an increase of 1 unit in `fscore` on `cc`  
controlled for `age.cat` `sex`

number of observations 1396

| Effect | 2.5% | 97.5% |
|--------|------|-------|
| 1.72   | 1.47 | 2.00  |

Test for no effects of exposure on 1 df: p-value= 6.2e-12

You can check for linearity of the log odds of being a case with `fscore` by comparing the model containing `freckles` as a factor with the model containing `freckles` as numeric.

```
> m1 <- glm(cc ~ freckles + age.cat + sex, family="binomial", data=mel)
> m2 <- glm(cc ~ fscore + age.cat + sex, family="binomial", data=mel)
> anova(m2, m1, test="Chisq")
Analysis of Deviance Table
```

```
Model 1: cc ~ fscore + age.cat + sex
Model 2: cc ~ freckles + age.cat + sex
 Resid. Df Resid. Dev Df Deviance Pr(>Chi)
1 1388 1738.6
2 1387 1737.1 1 1.5206 0.2175
```

There is no evidence against linearity ( $p = 0.22$ ).

It is sometimes helpful to look at the linearity in more detail with

```
> m1 <- glm(cc ~ C(freckles, contr.cum) + age.cat + sex, family="binomial", data=mel)
> round(ci.exp(m1), 2)
```

|                            | exp(Est.) | 2.5% | 97.5% |
|----------------------------|-----------|------|-------|
| (Intercept)                | 0.41      | 0.23 | 0.72  |
| C(freckles, contr.cum)some | 1.51      | 1.17 | 1.95  |
| C(freckles, contr.cum)many | 2.03      | 1.49 | 2.78  |
| age.cat[30,40)             | 0.90      | 0.49 | 1.67  |
| age.cat[40,50)             | 0.91      | 0.51 | 1.62  |
| age.cat[50,60)             | 0.97      | 0.54 | 1.75  |
| age.cat[60,70)             | 0.82      | 0.45 | 1.48  |
| age.cat[70,85)             | 0.89      | 0.48 | 1.65  |
| sexF                       | 0.94      | 0.74 | 1.19  |

```
> m2 <- glm(cc ~ fscore + age.cat + sex, family="binomial", data=mel)
> round(ci.exp(m2), 2)
```

|                | exp(Est.) | 2.5% | 97.5% |
|----------------|-----------|------|-------|
| (Intercept)    | 0.23      | 0.12 | 0.42  |
| fscore         | 1.72      | 1.47 | 2.00  |
| age.cat[30,40) | 0.90      | 0.49 | 1.67  |
| age.cat[40,50) | 0.91      | 0.51 | 1.63  |
| age.cat[50,60) | 0.97      | 0.54 | 1.75  |
| age.cat[60,70) | 0.81      | 0.45 | 1.47  |
| age.cat[70,85) | 0.89      | 0.48 | 1.66  |
| sexF           | 0.94      | 0.74 | 1.18  |

The use of `C(freckles, contr.cum)` makes each odds ratio to compare the odds at that level versus the previous level; not against the baseline (except for the 2nd level). If the log-odds are linear then these odds ratios should be the same (and the same as the odds ratio for `fscore` in `m2`).

### 2.8.13 Graphical displays

The odds ratios (with CIs) can be graphically displayed using function `plotEst()` in `Epi`. It uses the value of `ci.lin()` evaluated on the fitted model object. As the intercept and the effects of age and sex are of no interest, we shall drop the corresponding rows (the 7 first ones) from the matrix produced by `ci.lin()`, and the plot is based just on the 1st, 5th and the 6th column of this matrix:

```
> m <- glm(cc ~ nvsm4 + nvlar3 + age.cat + sex, family="binomial", data=mel)
> plotEst(exp(ci.lin(m)[2:5, -(2:4)]), xlog=T, vref=1)
```

The `xlog` argument makes the OR axis logarithmic.

## 2.9 Estimation of effects: simple and more complex

This exercise deals with analysis of metric and binary response variables. We start with simple estimation of effects of a binary, categorical or a numeric explanatory variable, the explanatory or exposure variable of interest. Then evaluation of potential modification and/or confounding by other variables is considered by stratification by and adjustment/control for these variables. Use of function `effx()` for such tasks is introduced together with functions `lm()` and `glm()` that can be used for more general linear and generalized linear models. Finally, more complex spline modelling for the effect of a numeric exposure variable is illustrated.

### 2.9.1 Response and explanatory variables

Identifying the *response* or *outcome variable* correctly is the key to analysis. The main types are:

- Metric or continuous (a measurement with units).
- Binary (“yes” vs. “no”, coded 1/0), or proportion.
- Failure in person-time, or incidence rate.

All these response variable are numeric.

Variables on which the response may depend are called *explanatory variables* or *regressors*. They can be categorical factors or numeric variables. A further important aspect of explanatory variables is the role they will play in the analysis.

- Primary role: exposure.
- Secondary role: confounder and/or effect-measure modifier.

The word “*effect*” is used here as a general term referring to ways of contrasting or comparing the expected values of the response variable at different levels of an explanatory variable. The main comparative measures or effect measures are:

- Differences in means for a metric response.
- Ratios of odds for a binary response.
- Ratios of rates for a failure or count response.

Other kinds of *contrasts* between exposure groups include (a) ratios of geometric means for positive-valued metric outcomes, (b) differences and ratios between proportions (risk difference and risk ratio), and (c) differences between incidence or mortality rates.

Note that in spite of using the causally loaded word “effect”, we treat *outcome regression* modelling here primarily with descriptive or predictive aims in mind. Traditionally, these types of models have also been used to estimate *causal effects* of exposure variables from the pertinent regression coefficients. More serious causal analysis is introduced in the lecture and practical on Saturday afternoon, and modern approaches to estimate causal effects will be considered on Tuesday afternoon.

## 2.9.2 Data set births

We shall use the `births` data to illustrate different aspects in estimating effects of various exposures on a metric response variable `bweight` = birth weight, recorded in grams.

1. Load the packages needed in this exercise and the data set, and look at its content

```
> library(Epi)
> library(mgcv)
> data(births)
> str(births)

'data.frame': 500 obs. of 8 variables:
 $ id : num 1 2 3 4 5 6 7 8 9 10 ...
 $ bweight: num 2974 3270 2620 3751 3200 ...
 $ lowbw : num 0 0 0 0 0 0 0 0 0 0 ...
 $ gestwks: num 38.5 NA 38.2 39.8 38.9 ...
 $ preterm: num 0 NA 0 0 0 0 0 0 0 0 ...
 $ matage : num 34 30 35 31 33 33 29 37 36 39 ...
 $ hyp : num 0 0 0 0 1 0 0 0 0 0 ...
 $ sex : num 2 1 2 1 1 2 2 1 2 1 ...
```

2. Because all variables are numeric we need first to do a little housekeeping. Two of them are directly converted into factors. Categorical versions of two continuous variables are created by function `cut()`.

```
> births$hyp <- factor(births$hyp, labels = c("Normo", "Hyper"))
> births$sex <- factor(births$sex, labels = c("M", "F"))
> births$agegrp <- cut(births$matage,
+ breaks = c(20, 25, 30, 35, 40, 45), right = FALSE)
> births$gest4 <- cut(births$gestwks,
+ breaks = c(20, 35, 37, 39, 45), right = FALSE)
```

3. Have a look at univariate summaries of the different variables in the data; especially the location and dispersion of the distribution of `bweight`.

```
> summary(births)

 id bweight lowbw gestwks preterm
Min. : 1.0 Min. : 628 Min. :0.00 Min. :24.69 Min. :0.0000
1st Qu.:125.8 1st Qu.:2862 1st Qu.:0.00 1st Qu.:37.94 1st Qu.:0.0000
Median :250.5 Median :3188 Median :0.00 Median :39.12 Median :0.0000
Mean :250.5 Mean :3137 Mean :0.12 Mean :38.72 Mean :0.1286
3rd Qu.:375.2 3rd Qu.:3551 3rd Qu.:0.00 3rd Qu.:40.09 3rd Qu.:0.0000
Max. :500.0 Max. :4553 Max. :1.00 Max. :43.16 Max. :1.0000
 NA's :10 NA's :10

 matage hyp sex agegrp gest4
Min. :23.00 Normo:428 M:264 [20,25): 2 [20,35): 31
1st Qu.:31.00 Hyper: 72 F:236 [25,30): 68 [35,37): 32
Median :34.00 [30,35):200 [37,39):167
Mean :34.03 [35,40):194 [39,45):260
3rd Qu.:37.00 [40,45): 36 NA's : 10
Max. :43.00

> with(births, sd(bweight))

[1] 637.4515
```

### 2.9.3 Simple estimation with `effx()`, `lm()` and `glm()`

We are ready to analyze the effect of `sex` on `bweight`. A binary explanatory variable, like `sex`, leads to an elementary two-group comparison of group means for a metric response.

1. Comparison of two groups is commonly done by the conventional *t*-test and the associated confidence interval.

```
> with(births, t.test(bweight ~ sex, var.equal=TRUE))

Two Sample t-test

data: bweight by sex
t = 3.4895, df = 498, p-value = 0.0005269
alternative hypothesis: true difference in means between group M and group F is not equal
95 percent confidence interval:
 86.11032 308.03170
sample estimates:
mean in group M mean in group F
 3229.902 3032.831
```

The *P*-value refers to the test of the null hypothesis that there is no effect of `sex` on birth weight (quite an uninteresting null hypothesis in itself!). However, `t.test()` does not provide the point estimate for the effect of `sex`; only the test result and a confidence interval.

2. The function `effx()` in `Epi` is intended to introduce the estimation of effects in epidemiology, together with the related ideas of stratification and controlling, i.e. adjustment for confounding, without the need for familiarity with statistical modelling. It is in fact a wrapper of function `glm()` that fits generalized linear models.
  - Now, let's do the same analysis with `effx()`

```
> effx(response=bweight, type="metric", exposure=sex, data=births)

response : bweight
type : metric
exposure : sex

sex is a factor with levels: M / F
baseline is M
effects are measured as differences in means

effect of sex on bweight
number of observations 500

Effect 2.5% 97.5%
-197.0 -308.0 -86.4

Test for no effects of exposure on 1 df: p-value= 0.000484
```

The estimated effect of `sex` on birth weight, measured as a difference in means between girls and boys, is  $-197$  g. Either the output from `t.test()` above or the command

```
> stat.table(sex, mean(bweight), data=births)
```

```

sex mean(bweight)

M 3229.90
F 3032.83

```

confirms this ( $3032.8 - 3229.9 = -197.1$ ).

3. The same task can easily be performed by `lm()` or by `glm()`. The main argument in both is the *model formula*, the left hand side being the response variable and the right hand side after “~” defines the explanatory variables and their joint effects on the response. Here the only explanatory variable is the binary factor `sex`. With `glm()` one specifies the `family`, i.e. the assumed distribution of the response variable, but in case you use `lm()`, this argument is not needed, because `lm()` fits only models for metric responses assuming Gaussian distribution.

```
> m1 <- glm(bweight ~ sex, family=gaussian, data=births)
> summary(m1)
```

Call:

```
glm(formula = bweight ~ sex, family = gaussian, data = births)
```

Coefficients:

```
 Estimate Std. Error t value Pr(>|t|)
(Intercept) 3229.90 38.80 83.244 < 2e-16 ***
sexF -197.07 56.48 -3.489 0.000527 ***
```

---

```
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for gaussian family taken to be 397442.7)
```

```
Null deviance: 202765853 on 499 degrees of freedom
Residual deviance: 197926455 on 498 degrees of freedom
AIC: 7869.3
```

```
Number of Fisher Scoring iterations: 2
```

Note the amount of output that `summary()` method produces. The point estimate plus confidence limits can, though, be concisely obtained by function `ci.lin()` found in `Epi` package.

```
> round(ci.lin(m1)[, c(1,5,6)] , 1)
```

```
 Estimate 2.5% 97.5%
(Intercept) 3229.9 3153.9 3305.9
sexF -197.1 -307.8 -86.4
```

4. Now, use `effx()` to find the effect of `hyp` (maternal hypertension) on `bweight`.



```

response : bweight
type : metric
exposure : hyp

hyp is a factor with levels: Normo / Hyper
baseline is Normo
effects are measured as differences in means

effect of hyp on bweight
number of observations 500

Effect 2.5% 97.5%
 -431 -585 -276

Test for no effects of exposure on 1 df: p-value= 4.9e-08

```

### 2.9.4 Factors on more than two levels

The variable `gest4` became as the result of cutting `gestwks` into 4 groups with left-closed and right-open boundaries [20,35) [35,37) [37,39) [39,45).

1. We shall find the effects of `gest4` on the metric response `bweight`.

```

> effx(response=bweight,typ="metric",exposure=gest4,data=births)

response : bweight
type : metric
exposure : gest4

gest4 is a factor with levels: [20,35) / [35,37) / [37,39) / [39,45)
baseline is [20,35)
effects are measured as differences in means

effect of gest4 on bweight
number of observations 490

 Effect 2.5% 97.5%
[35,37) vs [20,35) 857 620 1090
[37,39) vs [20,35) 1360 1180 1540
[39,45) vs [20,35) 1670 1490 1850

Test for no effects of exposure on 3 df: p-value= <2e-16

```

There are now 3 effect estimates:

```

[35,37) vs [20,35) 857
[37,39) vs [20,35) 1360
[39,45) vs [20,35) 1668

```

The command

```
> stat.table(gest4, mean(bweight), data=births)
```

```

gest4 mean(bweight)

[20,35) 1733.74
[35,37) 2590.31
[37,39) 3093.77
[39,45) 3401.26

```

confirms that the effect of `agegrp` (level 2 vs level 1) is  $2590 - 1733 = 857$ , etc.

2. Compute these estimates by `lm()` and find out how the coefficients are related to the group means

```
> m2 <- lm(bweight ~ gest4, data = births)
> round(ci.lin(m2)[, c(1,5,6)] , 1)
```

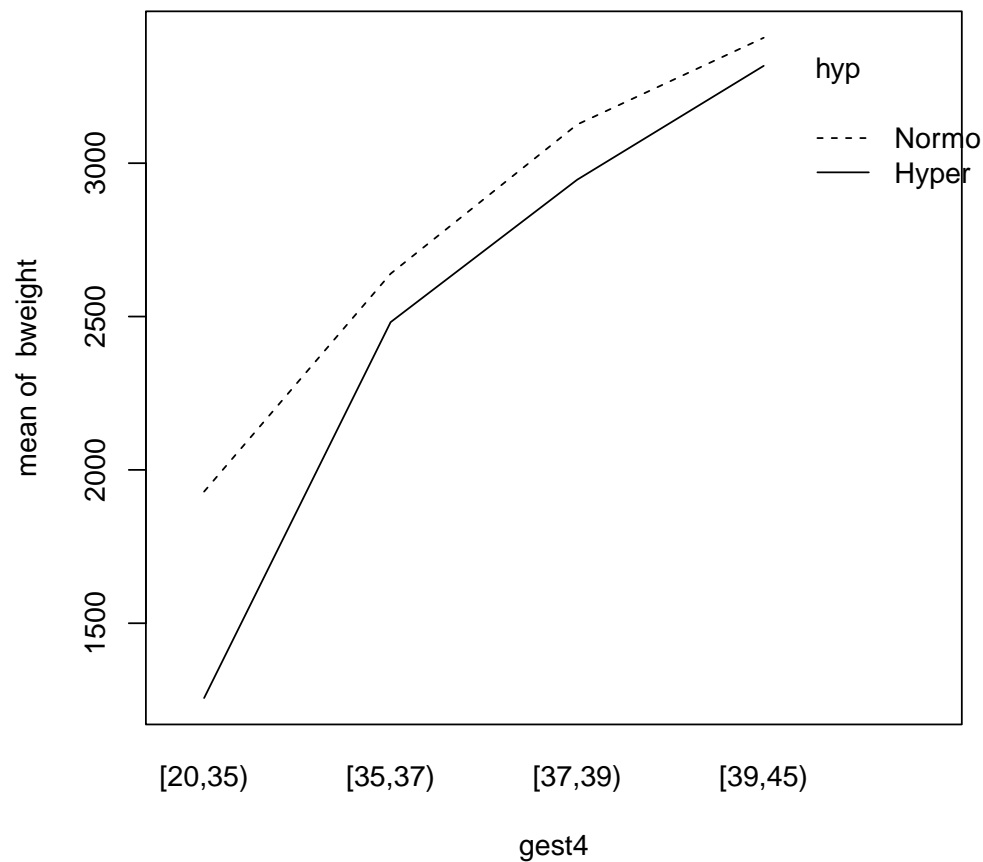
```
 Estimate 2.5% 97.5%
(Intercept) 1733.7 1565.3 1902.1
gest4[35,37) 856.6 620.3 1092.9
gest4[37,39) 1360.0 1176.7 1543.4
gest4[39,45) 1667.5 1489.4 1845.7
```

### 2.9.5 Stratified effects, and interaction or effect-measure modification

We shall now examine whether and to what extent the “effect” of `hyp` on `bweight`, i.e. the mean difference between hypertensive and normotensive mothers, varies by `gest4` without assigning causal interpretation to the estimated contrasts.

1. The following “interaction plot” shows how the mean `bweight` depends jointly on `hyp` and `gest4`

```
> par(mfrow=c(1,1))
> with(births, interaction.plot(gest4, hyp, bweight))
```



It appears that the mean difference in `bweight` between hypertensive and normotensive mothers is related to gestational age.

- Let us get numerical values for the mean differences in the different `gest4` categories:

```
> effx(bweight, type="metric", exposure=hyp, strata=gest4,data=births)
```

```

response : bweight
type : metric
exposure : hyp
stratified by : gest4
```

```
hyp is a factor with levels: Normo / Hyper
baseline is Normo
gest4 is a factor with levels: [20,35)/[35,37)/[37,39)/[39,45)
effects are measured as differences in means

```

```
effect of hyp on bweight
stratified by gest4
```

```
number of observations 490
```

```
Effect 2.5% 97.5%
```

```
strata [20,35) level Hyper vs Normo -673.0 -1040 -307.00
strata [35,37) level Hyper vs Normo -158.0 -510 195.00
strata [37,39) level Hyper vs Normo -180.0 -366 6.23
strata [39,45) level Hyper vs Normo -91.6 -298 114.00
```

```
Test for effect modification on 3 df: p-value= 0.0553
```

The estimated effects of `hyp` in the different strata defined by `gest4` thus range from about  $-100$  g among those with  $\geq 39$  weeks of gestation to about  $-700$  g among those with  $< 35$  weeks of gestation. The error margin especially around the latter estimate is quite wide, though. The  $P$ -value 0.055 from the test for *effect(-measure) modification* indicates weak evidence against the null hypothesis of “no interaction between `hyp` and `gest4`”. On the other hand, this test may well be not very sensitive given the small number of preterm babies in these data.

3. Stratified estimation of effects can also be done by `lm()`, and you should get the same results:

```
> m3 <- lm(bweight ~ gest4/hyp, data = births)
> round(ci.lin(m3)[, c(1,5,6)], 1)
```

|                       | Estimate | 2.5%    | 97.5%  |
|-----------------------|----------|---------|--------|
| (Intercept)           | 1929.1   | 1732.1  | 2126.2 |
| gest4[35,37)          | 710.5    | 431.9   | 989.2  |
| gest4[37,39)          | 1197.0   | 984.7   | 1409.3 |
| gest4[39,45)          | 1479.9   | 1273.9  | 1685.8 |
| gest4[20,35):hypHyper | -673.0   | -1038.8 | -307.3 |
| gest4[35,37):hypHyper | -158.0   | -510.5  | 194.5  |
| gest4[37,39):hypHyper | -180.1   | -366.4  | 6.2    |
| gest4[39,45):hypHyper | -91.6    | -297.5  | 114.4  |

4. An equivalent model with an explicit *product term* or *interaction term* between `gest4` and `hyp` is fitted as follows

```
> m3I <- lm(bweight ~ gest4 + hyp + gest4:hyp, data = births)
> round(ci.lin(m3I)[, c(1,5,6)], 1)
```

|                       | Estimate | 2.5%    | 97.5%  |
|-----------------------|----------|---------|--------|
| (Intercept)           | 1929.1   | 1732.1  | 2126.2 |
| gest4[35,37)          | 710.5    | 431.9   | 989.2  |
| gest4[37,39)          | 1197.0   | 984.7   | 1409.3 |
| gest4[39,45)          | 1479.9   | 1273.9  | 1685.8 |
| hypHyper              | -673.0   | -1038.8 | -307.3 |
| gest4[35,37):hypHyper | 515.0    | 7.1     | 1023.0 |
| gest4[37,39):hypHyper | 492.9    | 82.5    | 903.4  |
| gest4[39,45):hypHyper | 581.5    | 161.7   | 1001.2 |

From this output you would find a familiar estimate  $-673$  g for those  $< 35$  gestational weeks. The remaining coefficients are estimates of the interaction effects such that e.g.  $515 = -158 - (-673)$  g describes the contrast in the effect of `hyp` on `bweight` between those 35 to  $< 37$  weeks and those  $< 35$  weeks of gestation.

5. Perhaps a more appropriate reference level for the categorized gestational age would be the highest one. Changing the reference level, here to be the 4th category, can be done by `Relevel()` function in the `Epi` package, after which an equivalent interaction model is fitted, now using a shorter expression for it in the model formula:

```
> births$gest4b <- Relevel(births$gest4, ref = 4)
> m3Ib <- lm(bweight ~ gest4b*hyp, data = births)
> round(ci.lin(m3Ib)[, c(1,5,6)], 1)
```

|                        | Estimate | 2.5%    | 97.5%   |
|------------------------|----------|---------|---------|
| (Intercept)            | 3409.0   | 3349.1  | 3468.9  |
| gest4b[20,35)          | -1479.9  | -1685.8 | -1273.9 |
| gest4b[35,37)          | -769.3   | -975.3  | -563.4  |
| gest4b[37,39)          | -282.9   | -382.0  | -183.8  |
| hypHyper               | -91.6    | -297.5  | 114.4   |
| gest4b[20,35):hypHyper | -581.5   | -1001.2 | -161.7  |
| gest4b[35,37):hypHyper | -66.4    | -474.7  | 341.8   |
| gest4b[37,39):hypHyper | -88.5    | -366.3  | 189.2   |

Notice now the coefficient  $-91.6$  for `hyp`. It estimates the contrast "Hyper" vs. "Normo" on `bweight` among those with  $\geq 39$  weeks of gestation. The estimate  $-88.5$  g =  $-180.1 - (-91.6)$  g describes the additional effect of `hyp` in the category 37 to 38 weeks of gestation upon that in the reference class.

6. At this stage it is interesting to compare the results from the interaction models to those from the corresponding "main effects" model, in which the effect of `hyp` is assumed not to be modified by `gest4`:

```
> m3M <- lm(bweight ~ gest4 + hyp, data = births)
> round(ci.lin(m3M)[, c(1,5,6)], 1)
```

|              | Estimate | 2.5%   | 97.5%  |
|--------------|----------|--------|--------|
| (Intercept)  | 1792.1   | 1621.6 | 1962.6 |
| gest4[35,37) | 861.0    | 627.0  | 1095.1 |
| gest4[37,39) | 1337.8   | 1155.7 | 1519.9 |
| gest4[39,45) | 1626.2   | 1447.9 | 1804.4 |
| hypHyper     | -201.0   | -322.9 | -79.1  |

The estimate  $-201$  g describing the overall contrast between hypertensive and normotensive mothers is obtained as a weighted average of the stratum-specific estimates that were got by `effx()` above. This assumption or the "no interaction" null hypothesis can formally be tested by a common deviance test.

```
> anova(m3I, m3M)
```

Analysis of Variance Table

Model 1: `bweight ~ gest4 + hyp + gest4:hyp`

Model 2: `bweight ~ gest4 + hyp`

|   | Res.Df | RSS       | Df | Sum of Sq | F      | Pr(>F)    |
|---|--------|-----------|----|-----------|--------|-----------|
| 1 | 482    | 107195493 |    |           |        |           |
| 2 | 485    | 108883306 | -3 | -1687813  | 2.5297 | 0.05659 . |

---

Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1

The  $P$ -value is practically the same as before, when the interaction was tested in `effx()`. However, in spite of obtaining a “non-significant” result from this test, the possibility of a real effect-measure modification should not be ignored in this case.

7. Now, use `effx()` to stratify (i) the effect of `hyp` on `bweight` by `sex` and then (ii) perform the stratified analysis using the two ways of fitting an interaction model with `lm`.

```

response : bweight
type : metric
exposure : hyp
stratified by : sex

hyp is a factor with levels: Normo / Hyper
baseline is Normo
sex is a factor with levels: M/F
effects are measured as differences in means

effect of hyp on bweight
stratified by sex

number of observations 500

 Effect 2.5% 97.5%
strata M level Hyper vs Normo -496 -696 -297
strata F level Hyper vs Normo -380 -617 -142

Test for effect modification on 1 df: p-value= 0.462

 Estimate 2.5% 97.5%
(Intercept) 3310.7 3230.1 3391.4
sexF -231.2 -347.2 -115.3
sexM:hypHyper -496.4 -696.1 -296.6
sexF:hypHyper -379.8 -617.4 -142.2

 Estimate 2.5% 97.5%
(Intercept) 3310.7 3230.1 3391.4
sexF -231.2 -347.2 -115.3
hypHyper -496.4 -696.1 -296.6
sexF:hypHyper 116.6 -193.8 427.0
```

Look at the results. Is there evidence for the effect of `hyp` being modified by `sex`?

### 2.9.6 Controlling or adjusting for the effect of `hyp` for `sex`

The effect of `hyp` is *controlled for* – or *adjusted for* – `sex` by first looking at the estimated effects of `hyp` in the two strata defined by `sex`, and then combining these effects if they seem sufficiently similar. In this case the estimated effects were  $-496$  and  $-380$  which look quite similar (and the  $P$ -value against “no interaction” was quite large, too), so we can perhaps combine them, and control for `sex`.

1. The combining is done by declaring `sex` as a control variable:

```
> effx(bweight, type="metric", exposure=hyp, control=sex, data=births)

response : bweight
type : metric
exposure : hyp
control vars : sex

hyp is a factor with levels: Normo / Hyper
baseline is Normo
effects are measured as differences in means

effect of hyp on bweight
controlled for sex

number of observations 500

Effect 2.5% 97.5%
 -448 -601 -295

Test for no effects of exposure on 1 df: p-value= 9.07e-09
```

2. The same is done with `lm()` as follows:

```
> m4 <- lm(bweight ~ sex + hyp, data = births)
> ci.lin(m4)[, c(1,5,6)]

 Estimate 2.5% 97.5%
(Intercept) 3302.8845 3225.0823 3380.6867
sexF -214.9931 -322.4614 -107.5249
hypHyper -448.0817 -600.8911 -295.2723
```

The estimated effect of `hyp` on `bweight` controlled for `sex` is thus  $-448$  g. There can be more than one control variable, e.g. `control=list(sex, agegrp)`.

Many people go straight ahead and control for variables which are likely to confound the effect of exposure without bothering to stratify first, but usually it is useful to stratify first.

## 2.9.7 Numeric exposures

If we wished to study the effect of gestation time on the baby's birth weight then `gestwks` is a numeric exposure variable.

1. Assuming that the relationship of the response with `gestwks` is roughly linear (for a continuous response), we can estimate the linear effect of `gestwks`, both with `effx()` and with `lm()` as follows:

```
> effx(response=bweight, type="metric", exposure=gestwks, data=births)

response : bweight
type : metric
exposure : gestwks
```

```

gestwks is numeric
effects are measured as differences in means

effect of an increase of 1 unit in gestwks on bweight
number of observations 490

Effect 2.5% 97.5%
 197 180 214

Test for no effects of exposure on 1 df: p-value= <2e-16

> m5 <- lm(bweight ~ gestwks, data=births) ; ci.lin(m5)[, c(1,5,6)]

 Estimate 2.5% 97.5%
(Intercept) -4489.1398 -5157.2891 -3820.9905
gestwks 196.9726 179.7482 214.1971

```

We have fitted a simple linear regression model and obtained estimates of the two regression coefficient: **intercept** and **slope**. The linear effect of **gestwks** is thus estimated by the slope coefficient, which is 197 g per each additional week of gestation.

2. You cannot stratify by a numeric variable, but you can study the effects of a numeric exposure stratified by (say) **agegrp** with

```

> effx(bweight, type="metric", exposure=gestwks, strata=agegrp, data=births)

response : bweight
type : metric
exposure : gestwks
stratified by : agegrp

gestwks is numeric
agegrp is a factor with levels: [20,25)/[25,30)/[30,35)/[35,40)/[40,45)
effects are measured as differences in means

effect of an increase of 1 unit in gestwks on bweight
stratified by agegrp

number of observations 490

 Effect 2.5% 97.5%
strata [20,25) 85 -191 361
strata [25,30) 206 167 245
strata [30,35) 198 171 225
strata [35,40) 202 168 235
strata [40,45) 175 124 226

Test for effect modification on 4 df: p-value= 0.8

```

You can control/adjust for a numeric variable by putting it in the control list.

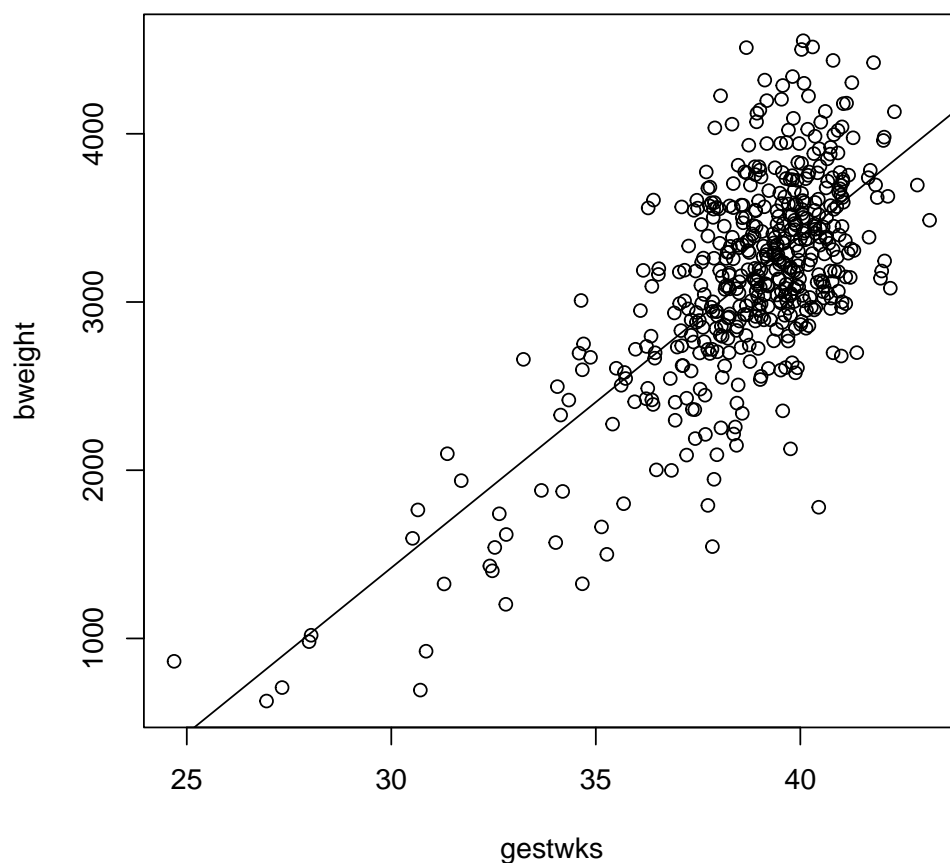


### 2.9.8 Checking the assumptions of the linear model

At this stage it will be best to make some visual check concerning our model assumptions using `plot()`. In particular, when the main argument for the *generic function* `plot()` is a fitted `lm` object, it will provide you some common diagnostic graphs.

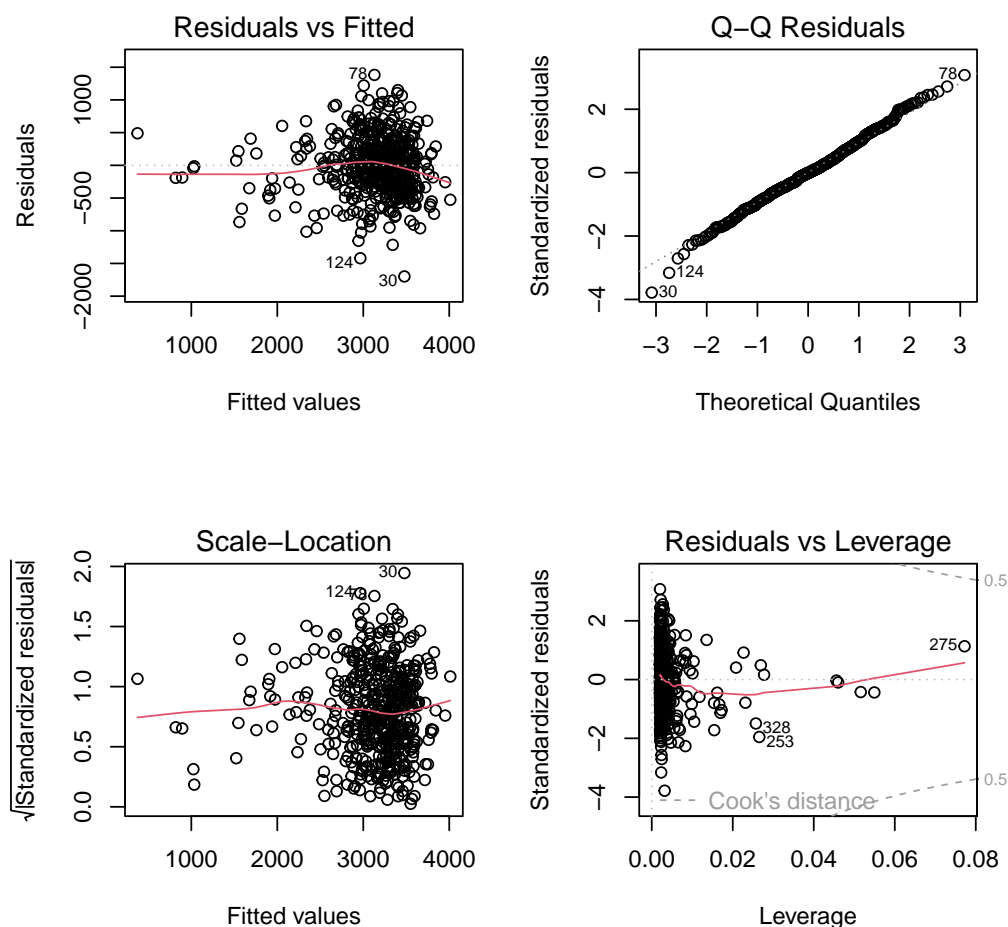
1. To check whether `bweight` goes up linearly with `gestwks` try

```
> with(births, plot(gestwks, bweight))
> abline(m5)
```



2. Moreover, take a look at the basic diagnostic plots for the fitted model.

```
> par(mfrow=c(2,2))
> plot(m5)
```



What can you say about the agreement with data of the assumptions of the simple linear regression model, like linearity of the systematic dependence, homoskedasticity and normality of the error terms?

### 2.9.9 Penalized spline model

We shall now continue the analysis such that the apparently curved effect of `gestwks` is modelled by a *penalized spline*, based on the recommendations of Martyn in his lecture of this morning.

You cannot fit a penalized spline model with `lm()` or `glm()`. Instead, function `gam()` in package `mgcv` can be used for this purpose. Make sure that you have loaded this package.

1. When calling `gam()`, the model formula contains expression '`s(X)`' for any explanatory variable `X`, for which you wish to fit a smooth function

```
> mPs <- gam(bweight ~ s(gestwks), data = births)
> summary(mPs)
```

```
Family: gaussian
Link function: identity
```

```
Formula:
```

```

bweight ~ s(gestwks)

Parametric coefficients:
 Estimate Std. Error t value Pr(>|t|)
(Intercept) 3138.01 20.11 156 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df F p-value
s(gestwks) 3.321 4.189 124.7 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.516 Deviance explained = 51.9%
GCV = 1.9995e+05 Scale est. = 1.9819e+05 n = 490

```

From the output given by `summary()` you find that the estimated intercept is equal to the overall mean birth weight in the data. The estimated residual variance is given by “Scale est.” or from subobject `sig2` of the fitted `gam` object. Taking square root you will obtain the estimated residual standard deviation: 445.2 g.

```

> mPs$sig2
[1] 198186

> sqrt(mPs$sig2)
[1] 445.1808

```

The degrees of freedom in this model are not computed as simply as in previous models, and they typically are not integer-valued. However, the fitted spline seems to consume only a little more degrees of freedom as an 3rd degree polynomial model would take.

2. A graphical presentation of the fitted curve together with the confidence and prediction intervals is more informative. Let us first write a short function script to facilitate the task. We utilize function `matshade()` in `Epi`, which creates shaded areas, and function `matlines()` which draws lines joining the pertinent end points over the  $x$ -values for which the predictions are computed.

```

> plotFitPredInt <- function(xval, fit, pred, ...)
+ {
+ matshade(xval, fit, lwd=2, alpha=0.2)
+ matshade(xval, pred, lwd=2, alpha=0.2)
+ matlines(xval, fit, lty=1, lwd=c(3,2,2), col=c("red","blue","blue"))
+ matlines(xval, pred, lty=1, lwd=c(3,2,2), col=c("red","green","green"))
+ }

```

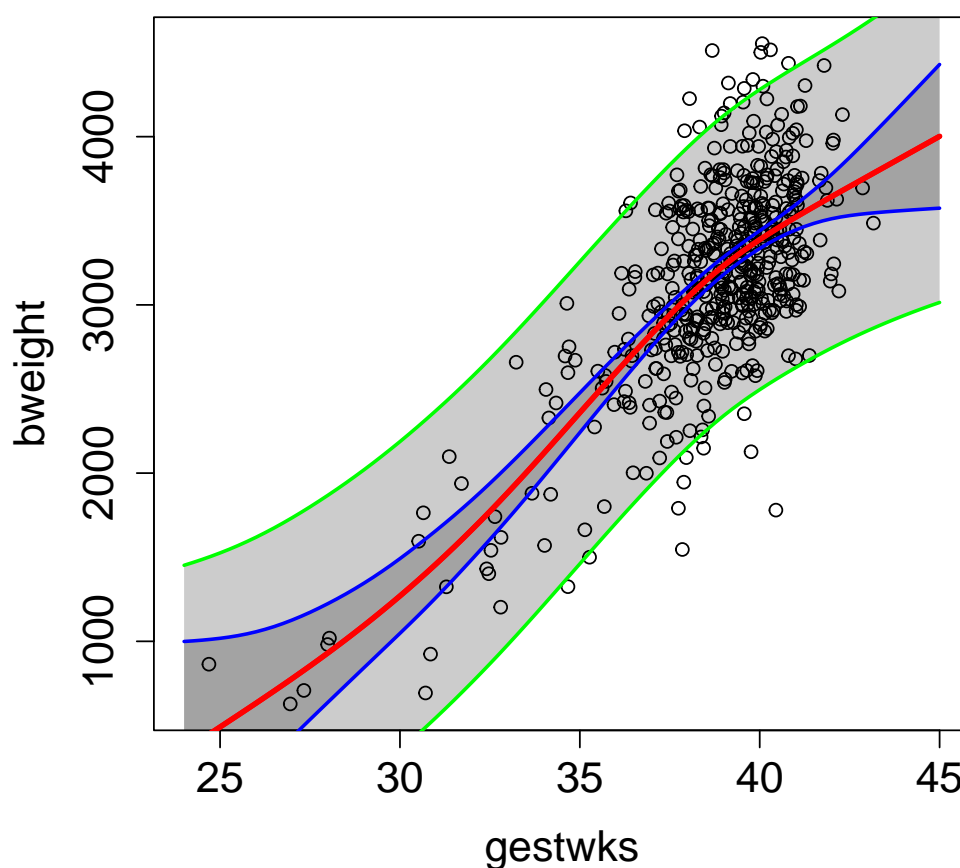
3. Finally, create a vector of  $x$ -values and compute the fitted/predicted values as well as the interval limits at these points from the fitted model object utilizing function `predict()`. This function creates a matrix of three columns: (1) fitted/predicted values, (2) lower limits, (3) upper limits and make the graph:

```
> nd <- data.frame(gestwks = seq(24, 45, by = 0.25))
> pr.Ps <- predict(mPs, newdata=nd, se.fit=TRUE)
> str(pr.Ps) # with se.fit=TRUE, only two columns: fitted value and its SE
```

```
List of 2
```

```
$ fit : num [1:85(1d)] 350 385 421 456 491 ...
..- attr(*, "dimnames")=List of 1
.. ..$: chr [1:85] "1" "2" "3" "4" ...
$ se.fit: num [1:85(1d)] 324 309 293 278 264 ...
..- attr(*, "dimnames")=List of 1
.. ..$: chr [1:85] "1" "2" "3" "4" ...
```

```
> fit.Ps <- cbind(pr.Ps$fit,
+ pr.Ps$fit - 2*pr.Ps$se.fit,
+ pr.Ps$fit + 2*pr.Ps$se.fit)
> pred.Ps <- cbind(pr.Ps$fit, # must add residual variance to se.fit^2
+ pr.Ps$fit - 2*sqrt(pr.Ps$se.fit^2 + mPs$sig2),
+ pr.Ps$fit + 2*sqrt(pr.Ps$se.fit^2 + mPs$sig2))
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim=c(24, 45),
+ cex.axis=1.5, cex.lab=1.5))
> plotFitPredInt(nd$gestwks, fit.Ps, pred.Ps)
```



Compare this with the graph on slide 20 of the lecture we had. Are you happy with the end result?

### 2.9.10 Analysis of binary outcomes

Instead of investigating the distribution and determinants of birth weight as such, it is common in perinatal epidemiology to consider occurrence of low birth weight; whether birth weight is  $< 2.5$  kg or not. Variable `lowbw` with values 1 and 0 in the `births` data represents that dichotomy. Let's perform some analyses on that outcome to illustrate effect estimation and modelling binary outcome.

1. We start with simple tabulation of the prevalence of `lowbw` by maternal hypertension

```
> stat.table(index=list(hyp, lowbw),
+ contents=list(count(), percent(lowbw)),
+ margins=TRUE, data=births)
```

| -----lowbw----- |      |      |       |
|-----------------|------|------|-------|
| hyp             | 0    | 1    | Total |
| -----           |      |      |       |
| Normo           | 388  | 40   | 428   |
|                 | 90.7 | 9.3  | 100.0 |
| Hyper           | 52   | 20   | 72    |
|                 | 72.2 | 27.8 | 100.0 |
| -----           |      |      |       |
| Total           | 440  | 60   | 500   |
|                 | 88.0 | 12.0 | 100.0 |
| -----           |      |      |       |

It seems that the prevalence for hypertensive mothers is about 18 percent points higher, or about three times as high as that for normotensive mothers,

2. The three comparative measures of prevalences can be obtained by `glm()`, whereas `effx()` gives only odds ratio:

```
> binRD <- glm(lowbw ~ hyp, family=binomial(link="identity"), data=births)
> round(ci.lin(binRD)[, c(1,2,5:6)], 3)
```

|             | Estimate | StdErr | 2.5%  | 97.5% |
|-------------|----------|--------|-------|-------|
| (Intercept) | 0.093    | 0.014  | 0.066 | 0.121 |
| hypHyper    | 0.184    | 0.055  | 0.077 | 0.291 |

```
> binRR <- glm(lowbw ~ hyp, family=binomial(link="log"), data=births)
> round(ci.lin(binRR, Exp=TRUE)[, c(1,2,5:7)], 3)
```

|             | Estimate | StdErr | exp(Est.) | 2.5%  | 97.5% |
|-------------|----------|--------|-----------|-------|-------|
| (Intercept) | -2.370   | 0.151  | 0.093     | 0.070 | 0.126 |
| hypHyper    | 1.089    | 0.242  | 2.972     | 1.848 | 4.780 |

```
> binOR <- glm(lowbw ~ hyp, family=binomial(link="logit"), data=births)
> round(ci.lin(binOR, Exp=TRUE)[, c(1,2,5:7)], 3)
```

|             | Estimate | StdErr | exp(Est.) | 2.5%  | 97.5% |
|-------------|----------|--------|-----------|-------|-------|
| (Intercept) | -2.272   | 0.166  | 0.103     | 0.074 | 0.143 |
| hypHyper    | 1.317    | 0.311  | 3.731     | 2.027 | 6.865 |

```
> effx(response=lowbw, type="binary", exposure=hyp, data=births)
```

```

response : lowbw
type : binary
exposure : hyp

```

```
hyp is a factor with levels: Normo / Hyper
baseline is Normo
effects are measured as odds ratios

```

```
effect of hyp on lowbw
number of observations 500
```

```
Effect 2.5% 97.5%
 3.73 2.03 6.87
```

```
Test for no effects of exposure on 1 df: p-value= 6.06e-05
```

Check that these results were quite compatible with the “about” estimates given in the previous item. How well is the odds ratio approximating the risk ratio here?

3. The prevalence of low birth weight is expected to be inversely related to gestational age (weeks), as is evident from simple tabulation

```
> stat.table(index=list(gest4, lowbw),
+ contents=list(count(), percent(lowbw)),
+ margins=TRUE, data=births)
```

```

-----lowbw-----
gest4 0 1 Total

[20,35) 6 25 31
 19.4 80.6 100.0

[35,37) 19 13 32
 59.4 40.6 100.0

[37,39) 149 18 167
 89.2 10.8 100.0

[39,45) 257 3 260
 98.8 1.2 100.0

Total 440 60 500
 88.0 12.0 100.0

```

4. Let's jump right away to spline modelling of this relationship

```
> binm1 <- gam(lowbw ~ s(gestwks), family=binomial(link="logit"), data=births)
> summary(binm1)
```

```
Family: binomial
Link function: logit
```

```

Formula:
lowbw ~ s(gestwks)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) -2.8665 0.2364 -12.12 <2e-16 ***

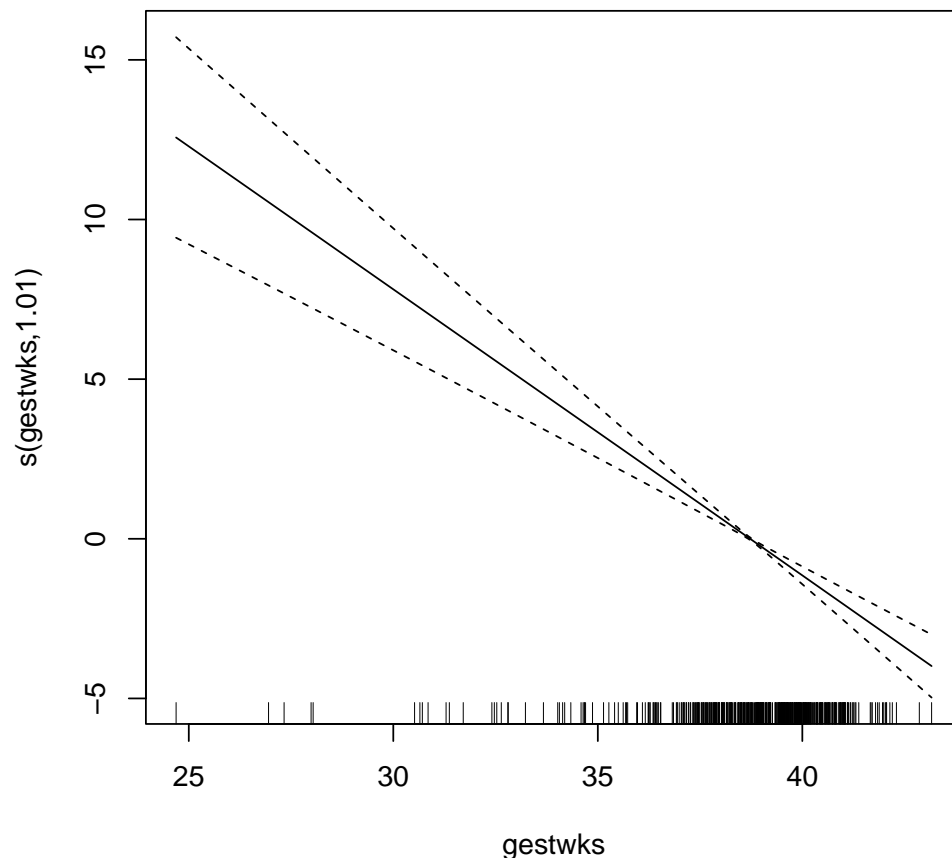
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(gestwks) 1.01 1.021 68.86 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.425 Deviance explained = 42.9%
UBRE = -0.57194 Scale est. = 1 n = 490
> plot(binm1)

```



Inspect the output. Would you agree, that the logit of the prevalence of outcome is almost linearly dependent on `gestwks`?

5. Encouraged by the result of the previous item, we continue the analysis with `glm()` and assuming logit-linearity

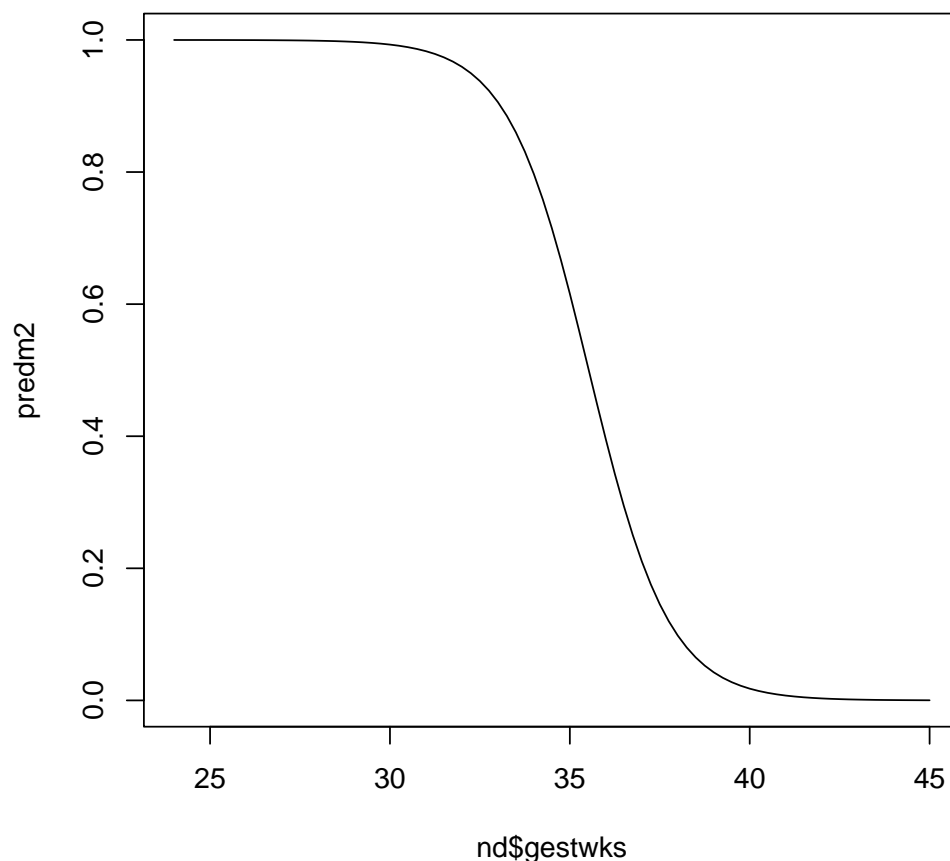
```
> binm2 <- glm(lowbw ~ I(gestwks-40), family=binomial(link="logit"), data=births)
> round(ci.lin(binm2, Exp=TRUE)[, c(1,2,5:7)], 3)
```

|                 | Estimate | StdErr | exp(Est.) | 2.5%  | 97.5% |
|-----------------|----------|--------|-----------|-------|-------|
| (Intercept)     | -4.011   | 0.338  | 0.018     | 0.009 | 0.035 |
| I(gestwks - 40) | -0.896   | 0.108  | 0.408     | 0.330 | 0.505 |

Inspect the results. How do you interpret the estimated coefficients and their exponentiated values?

6. Instead of fitted logits, it can be more informative to plot the fitted prevalences against `gestwks`, in which we utilize the previously created data frame `nd`

```
> predm2 <- predict(binm2, newdata=nd, type="response")
> plot(nd$gestwks, predm2, type="l")
```



The curve seems to cover practically the whole range of the outcome probability scale with a relatively steep slope between about 33 to 37 weeks.

7. As with numeric birth weight, it may be of interest, whether the effect of `gestwks` is modified by maternal hypertension, so let's fit an interaction model and view the results



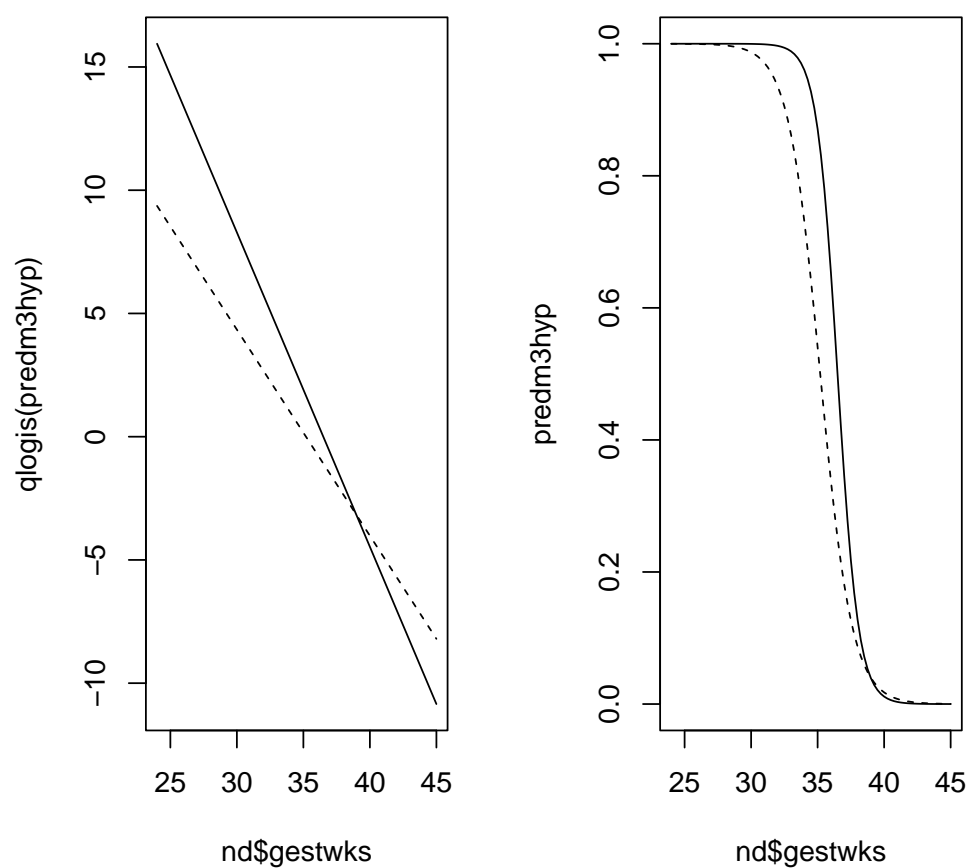
```
> binm3 <- glm(lowbw ~ hyp*I(gestwks-40), family=binomial, data=births)
> round(ci.lin(binm3, Exp=TRUE)[, c(1,2,5:7)], 3)
```

|                          | Estimate | StdErr | exp(Est.) | 2.5%  | 97.5% |
|--------------------------|----------|--------|-----------|-------|-------|
| (Intercept)              | -4.019   | 0.364  | 0.018     | 0.009 | 0.037 |
| hypHyper                 | -0.449   | 1.173  | 0.638     | 0.064 | 6.355 |
| I(gestwks - 40)          | -0.836   | 0.113  | 0.433     | 0.347 | 0.541 |
| hypHyper:I(gestwks - 40) | -0.439   | 0.402  | 0.645     | 0.293 | 1.417 |

How would you interpret the coefficients and their antilogarithms here?

- Even though there seems to be no sufficient evidence for effect-measure modification, it can be of interest to compare both the fitted lines on the logit scale and the fitted curves on the probability scale between the two groups. Function `qlogis()` returns the value of the logit transformation of the given argument.

```
> predm3hyp <- predict(binm3,
+ newdata=data.frame(hyp="Hyper", nd), type="response")
> predm3nor <- predict(binm3,
+ newdata=data.frame(hyp="Normo", nd), type="response")
> par(mfrow=c(1,2))
> plot(nd$gestwks, qlogis(predm3hyp), type="l")
> lines(nd$gestwks, qlogis(predm3nor), lty=2)
> plot(nd$gestwks, predm3hyp, type="l")
> lines(nd$gestwks, predm3nor, lty=2)
```



The

logit-line starts from a higher level and its slope is steeper for the hypertensive mothers, which sounds reasonable. However, the two lines appear to cross at about 38 weeks. On the other hand, the vertical difference of the two probability curves appears discernible only in the area from about 32 to 38 weeks of gestation

When interpreting these findings, one needs to keep in mind that the precision of these curves is very low, because of the small number of outcome cases overall.

## 2.10 Estimation and reporting of curved effects

This exercise deals with modelling of curved effects of continuous explanatory variables both on a metric response assuming the Gaussian distribution and on a count or rate outcome based on the Poisson family.

In the first part we continue our analysis on gestational age on birth weight focussing on fitting spline models, both unpenalized and a penalized one.

In the second part we analyse the `testisDK` data found in the `Epi` package. It contains the numbers of cases of testis cancer and mid-year populations (person-years) in 1-year age groups in Denmark during 1943–96. In this analysis we apply Poisson regression on the incidence rates treating age and calendar time, first as categorical but then fitting a penalized spline model.

### 2.10.1 Data births: Simple linear regression and 3rd degree polynomial

Recall what was done in items 17 to 24 of the Exercise on simple estimation of effects, in which a simple linear regression and a 3rd degree polynomial were fitted. The main results are also shown on slides 6, 8, 9, and 20 of the lecture on linear models.

1. Make a basic scatter plot and draw the fitted line from a simple linear regression on it.

```
> library(Epi)
> data(births)
> par(mfrow=c(1,1))
> with(births, plot(gestwks, bweight))
> mlin <- lm(bweight ~ gestwks, data = births)
> abline(mlin)
```

2. Repeat also the diagnostic plots of this simple model

```
> par(mfrow=c(2,2))
> plot(mlin)
```

Some deviation from the linear model is apparent.

### 2.10.2 Fitting a natural cubic spline

A popular approach for flexible modelling is based on natural regression splines, which have more reasonable tail behaviour than polynomial regression.

3. By the following piece of code you can fit a *natural cubic spline* with 5 pre-specified knots to be put at 28, 34, 38, 40 and 43 weeks of gestation, respectively, determining the degree of smoothing.

```
> library(splines)
> mNs5 <- lm(bweight ~ Ns(gestwks, knots = c(28,34,38,40,43)),
+ data = births)
> round(ci.exp(mNs5, Exp=FALSE), 1)
```

|                                             | Estimate | 2.5%   | 97.5%  |
|---------------------------------------------|----------|--------|--------|
| (Intercept)                                 | 987.1    | 696.2  | 1278.1 |
| Ns(gestwks, knots = c(28, 34, 38, 40, 43))1 | 1996.9   | 1678.0 | 2315.8 |
| Ns(gestwks, knots = c(28, 34, 38, 40, 43))2 | 2234.2   | 2005.2 | 2463.2 |
| Ns(gestwks, knots = c(28, 34, 38, 40, 43))3 | 3271.0   | 2618.1 | 3924.0 |
| Ns(gestwks, knots = c(28, 34, 38, 40, 43))4 | 2265.8   | 1886.3 | 2645.3 |

These regression coefficients are even less interpretable than those in the polynomial model.

4. A graphical presentation of the fitted curve together with the confidence and prediction intervals is more informative. As this kind of presentation will be repeated, let us write a short function script to facilitate the task. We utilize function `matshade()` in `Epi`, which creates shaded areas, and function `matlines()` which draws lines joining the pertinent end points over the  $x$ -values for which the predictions are computed.

```
> plotFitPredInt <- function(xval, fit, pred, ...)
+ {
+ matshade(xval, fit, lwd=2, alpha=0.2)
+ matshade(xval, pred, lwd=2, alpha=0.2)
+ matlines(xval, fit, lty=1, lwd=c(3,2,2), col=c("red","blue","blue"))
+ matlines(xval, pred, lty=1, lwd=c(3,2,2), col=c("red","green","green"))
+ }
```

5. Now, create a vector of  $x$ -values and compute the fitted/predicted values as well as the interval limits at these points from the fitted model object utilizing function `predict()`. This function creates a matrix of three columns: (1) fitted/predicted values, (2) lower limits, (3) upper limits

```
> nd <- data.frame(gestwks = seq(24, 45, by = 0.25))
> fit.Ns5 <- predict(mNs5, newdata=nd, interval="conf")
> pred.Ns5 <- predict(mNs5, newdata=nd, interval="pred")
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim=c(23, 46),
+ cex.axis=1.5, cex.lab=1.5))
> plotFitPredInt(xval=nd$gestwks, fit=fit.Ns5, pred=pred.Ns5)
```

Compare this with the 3rd order curve previously fitted (see slide 20 of the lecture). In a natural spline the curve is constrained to be linear beyond the extreme knots.

6. Take a look at the basic diagnostic plots from the spline model.

```
> par(mfrow=c(2,2))
> plot(mNs5)
```

How would you interpret these plots?

The choice of the number of knots and their locations can be quite arbitrary, and the results are often sensitive to these choices.

7. To illustrate arbitrariness and associated problems with specification of knots, you may now fit another natural spline model like the one above but now with 10 knots at the following sequence of points: `seq(25, 43, by = 2)`. Display graphically the results

```

> mNs10 <- lm(bweight ~ Ns(gestwks,
+ knots = seq(25, 43, by = 2)), data = births)
> round(ci.lin(mNs10)[, c(1,5,6)], 1)

 Estimate 2.5% 97.5%
(Intercept) 799.9 48.7 1551.1
Ns(gestwks, knots = seq(25, 43, by = 2))1 692.5 -1453.2 2838.3
Ns(gestwks, knots = seq(25, 43, by = 2))2 467.2 -620.5 1554.9
Ns(gestwks, knots = seq(25, 43, by = 2))3 989.9 1.8 1978.0
Ns(gestwks, knots = seq(25, 43, by = 2))4 1608.1 762.9 2453.3
Ns(gestwks, knots = seq(25, 43, by = 2))5 1989.6 1202.3 2776.9
Ns(gestwks, knots = seq(25, 43, by = 2))6 2515.0 1745.8 3284.2
Ns(gestwks, knots = seq(25, 43, by = 2))7 2796.4 2089.2 3503.7
Ns(gestwks, knots = seq(25, 43, by = 2))8 2508.1 796.7 4219.4
Ns(gestwks, knots = seq(25, 43, by = 2))9 3117.4 2204.7 4030.1

> fit.Ns10 <- predict(mNs10, newdata=nd, interval="conf")
> pred.Ns10 <- predict(mNs10, newdata=nd, interval="pred")
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim = c(23, 46),
+ cex.axis= 1.5, cex.lab = 1.5))
> plotFitPredInt(nd$gestwks, fit.Ns10, pred.Ns10)

```

The behaviour of the curve is really wild for small values of `gestwks`!

### 2.10.3 Penalized spline model

One way to go around the arbitrariness in the specification of knots is to fit a *penalized spline* model, which imposes a “roughness penalty” on the curve. Even though a big number of knots are initially allowed, the resulting fitted curve will be optimally smooth.

You cannot fit a penalized spline model with `lm()` or `glm()`, Instead, function `gam()` in package `mgcv` can be used for this purpose.

8. You must first load package `mgcv`.
9. When calling `gam()`, the model formula contains expression '`s(X)`' for any explanatory variable `X`, for which you wish to fit a smooth function

```

> library(mgcv)
> mPs <- gam(bweight ~ s(gestwks), data = births)
> summary(mPs)

Family: gaussian
Link function: identity

Formula:
bweight ~ s(gestwks)

Parametric coefficients:
 Estimate Std. Error t value Pr(>|t|)
(Intercept) 3138.01 20.11 156 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df F p-value
s(gestwks) 3.321 4.189 124.7 <2e-16 ***

```

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.516 Deviance explained = 51.9%
GCV = 1.9995e+05 Scale est. = 1.9819e+05 n = 490

```

From the output given by `summary()` you find that the estimated intercept is here, too, equal to the overall mean birth weight in the data. The estimated residual variance is given by “Scale est.” or from subobject `sig2` of the fitted `gam` object. Taking square root you will obtain the estimated residual standard deviation: 445.2 g.

```

> mPs$sig2

[1] 198186

> sqrt(mPs$sig2)

[1] 445.1808

```

The degrees of freedom in this model are not computed as simply as in previous models, and they typically are not integer-valued. However, the fitted spline seems to consume only a little more degrees of freedom as the 3rd degree polynomial above.

10. As in previous models we shall plot the fitted curve together with 95 % confidence intervals for the mean responses and 95 % prediction intervals for individual responses. Obtaining the prediction intervals from the fitted `gam` object requires a bit more work than with `lm` objects.

```

> pr.Ps <- predict(mPs, newdata=nd, se.fit=TRUE)
> str(pr.Ps) # with se.fit=TRUE, only two columns: fitted value and its SE

List of 2
 $ fit : num [1:85(1d)] 350 385 421 456 491 ...
 .. attr(*, "dimnames")=List of 1
 $: chr [1:85] "1" "2" "3" "4" ...
 $ se.fit: num [1:85(1d)] 324 309 293 278 264 ...
 .. attr(*, "dimnames")=List of 1
 $: chr [1:85] "1" "2" "3" "4" ...

> fit.Ps <- cbind(pr.Ps$fit,
+ pr.Ps$fit - 2*pr.Ps$se.fit,
+ pr.Ps$fit + 2*pr.Ps$se.fit)
> pred.Ps <- cbind(pr.Ps$fit, # must add residual variance to se.fit^2
+ pr.Ps$fit - 2*sqrt(pr.Ps$se.fit^2 + mPs$sig2),
+ pr.Ps$fit + 2*sqrt(pr.Ps$se.fit^2 + mPs$sig2))
> par(mfrow=c(1,1))
> with(births, plot(bweight ~ gestwks, xlim=c(24, 45),
+ cex.axis=1.5, cex.lab=1.5))
> plotFitPredInt(nd$gestwks, fit.Ps, pred.Ps)

```

The fitted curve is indeed clearly more reasonable than the polynomial.

### 2.10.4 Testis cancer: Data input and housekeeping

We shall now switch to analyzing the incidence of testis cancer in Denmark during 1943–1998 by age and calendar time or period.

11. Load the data and inspect its structure:

```
> library(Epi)
> data(testisDK)
> str(testisDK)

'data.frame': 4860 obs. of 4 variables:
 $ A: num 0 1 2 3 4 5 6 7 8 9 ...
 $ P: num 1943 1943 1943 1943 1943 ...
 $ D: num 1 1 0 1 0 0 0 0 0 0 ...
 $ Y: num 39650 36943 34588 33267 32614 ...

> summary(testisDK)

 A P D Y
Min. : 0.0 Min. :1943 Min. : 0.000 Min. : 471.7
1st Qu.:22.0 1st Qu.:1956 1st Qu.: 0.000 1st Qu.:18482.2
Median :44.5 Median :1970 Median : 1.000 Median :28636.0
Mean :44.5 Mean :1970 Mean : 1.812 Mean :26239.8
3rd Qu.:67.0 3rd Qu.:1983 3rd Qu.: 2.000 3rd Qu.:36785.5
Max. :89.0 Max. :1996 Max. :17.000 Max. :47226.8

> head(testisDK)

 A P D Y
1 0 1943 1 39649.50
2 1 1943 1 36942.83
3 2 1943 0 34588.33
4 3 1943 1 33267.00
5 4 1943 0 32614.00
6 5 1943 0 32020.33
```

12. There are nearly 5000 observations from 90 one-year age groups and 54 calendar years. To get a clearer picture of what's going on we do some housekeeping. The age range will be limited to 15–79 years, and age and period are both categorised into 5-year intervals – according to the time-honoured practice in epidemiology.

```
> tdk <- subset(testisDK, A > 14 & A < 80)
> tdk$Age <- cut(tdk$A, br = 5*(3:16), include.lowest=TRUE, right=FALSE)
> nAge <- length(levels(tdk$Age))
> tdk$Per <- cut(tdk$P, br = seq(1943,1998,by=5),
+ include.lowest=TRUE, right=FALSE)
> nPer <- length(levels(tdk$Per))
```

### 2.10.5 Some descriptive analysis

Computation and tabulation of incidence rates

13. Tabulate numbers of cases and person-years, and compute the incidence rates (per 100,000 y) in each 5 y × 5 y cell using `stat.table()`

```

> tab <- stat.table(index = list(Age, Per),
+ contents = list(D = sum(D),
+ Y = sum(Y/1000),
+ rate = ratio(D, Y, 10^5)),
+ margins = TRUE,
+ data = tdk)
> print(tab, digits=c(sum=0, ratio=1))

```

|         | -----Per----- |             |             |             |             |             |             |
|---------|---------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Age     | [1943,1948)   | [1948,1953) | [1953,1958) | [1958,1963) | [1963,1968) | [1968,1973) | [1973,1978) |
| [15,20) | 10            | 7           | 13          | 13          | 15          | 33          |             |
|         | 774           | 744         | 794         | 973         | 1052        | 961         |             |
|         | 1.3           | 0.9         | 1.6         | 1.3         | 1.4         | 3.4         |             |
| [20,25) | 30            | 31          | 46          | 49          | 55          | 85          |             |
|         | 813           | 745         | 722         | 771         | 960         | 1054        |             |
|         | 3.7           | 4.2         | 6.4         | 6.4         | 5.7         | 8.1         |             |
| [25,30) | 55            | 62          | 63          | 82          | 87          | 103         |             |
|         | 791           | 782         | 723         | 699         | 765         | 963         |             |
|         | 7.0           | 7.9         | 8.7         | 11.7        | 11.4        | 10.7        |             |
| [30,35) | 56            | 66          | 82          | 88          | 103         | 124         |             |
|         | 799           | 775         | 769         | 712         | 700         | 770         |             |
|         | 7.0           | 8.5         | 10.7        | 12.4        | 14.7        | 16.1        |             |
| [35,40) | 53            | 56          | 56          | 67          | 99          | 124         |             |
|         | 769           | 783         | 760         | 760         | 712         | 702         |             |
|         | 6.9           | 7.2         | 7.4         | 8.8         | 13.9        | 17.7        |             |
| [40,45) | 35            | 47          | 65          | 64          | 67          | 85          |             |
|         | 694           | 754         | 768         | 750         | 757         | 710         |             |
|         | 5.0           | 6.2         | 8.5         | 8.5         | 8.9         | 12.0        |             |
| [45,50) | 29            | 30          | 37          | 54          | 45          | 64          |             |
|         | 622           | 677         | 738         | 753         | 738         | 746         |             |
|         | 4.7           | 4.4         | 5.0         | 7.2         | 6.1         | 8.6         |             |
| [50,55) | 16            | 28          | 22          | 27          | 46          | 36          |             |
|         | 539           | 600         | 654         | 715         | 733         | 718         |             |
|         | 3.0           | 4.7         | 3.4         | 3.8         | 6.3         | 5.0         |             |
| [55,60) | 6             | 14          | 16          | 25          | 26          | 29          |             |
|         | 471           | 513         | 571         | 623         | 681         | 698         |             |
|         | 1.3           | 2.7         | 2.8         | 4.0         | 3.8         | 4.2         |             |
| [60,65) | 9             | 12          | 11          | 13          | 20          | 18          |             |
|         | 403           | 435         | 475         | 528         | 573         | 627         |             |
|         | 2.2           | 2.8         | 2.3         | 2.5         | 3.5         | 2.9         |             |
| [65,70) | 13            | 9           | 10          | 13          | 8           | 8           |             |
|         | 328           | 358         | 386         | 420         | 463         | 501         |             |
|         | 4.0           | 2.5         | 2.6         | 3.1         | 1.7         | 1.6         |             |
| [70,75) | 9             | 6           | 5           | 7           | 8           | 16          |             |
|         | 230           | 269         | 295         | 317         | 342         | 374         |             |
|         | 3.9           | 2.2         | 1.7         | 2.2         | 2.3         | 4.3         |             |



|         |                    |                    |                    |                    |                    |                    |
|---------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| [75,80] | 6<br>140<br>4.3    | 3<br>167<br>1.8    | 7<br>196<br>3.6    | 11<br>215<br>5.1   | 6<br>229<br>2.6    | 8<br>246<br>3.2    |
| Total   | 327<br>7375<br>4.4 | 371<br>7601<br>4.9 | 433<br>7851<br>5.5 | 513<br>8236<br>6.2 | 585<br>8703<br>6.7 | 733<br>9070<br>8.1 |

---

Look at the incidence rates in the column margin and in the row margin. In which age group is the marginal age-specific rate highest? Do the period-specific marginal rates have any trend over time?

14. From the saved table object `tab` you can plot an age-incidence curve for each period separately, after you have checked the structure of the table, so that you know the relevant dimensions in it. There is a function `rateplot()` in `Epi` that does default plotting of tables of rates (see the help page of `rateplot`)

```
> str(tab)

' stat.table' num [1:3, 1:14, 1:12] 10 773.81 1.29 30 813.02 ...
- attr(*, "dimnames")=List of 3
..$ contents: Named chr [1:3] "D" "Y" "rate"
..$ Age : chr [1:14] "[15,20)" "[20,25)" "[25,30)" "[30,35)" ...
..$ Per : chr [1:12] "[1943,1948)" "[1948,1953)" "[1953,1958)" "[1958,1963)" ...
- attr(*, "table.fun")= chr [1:3] "sum" "sum" "ratio"

> par(mfrow=c(1,1))
> rateplot(rates=tab[3, 1:nAge, 1:nPer], which="ap", ylim=c(1,30),
+ age=seq(15, 75, 5), per=seq(1943, 1993, 5),
+ col=heat.colors(16), ann=TRUE)
```

Is there any common pattern in the age-incidence curves across the periods?

### 2.10.6 Age and period as categorical factors

We shall first fit a Poisson regression model with log link on age and period model in the traditional way, in which both factors are treated as categorical. The model is additive on the log-rate scale. It is useful to scale the person-years to be expressed in  $10^5$  y.

```
15. > tdk$Y <- tdk$Y/100000
> mCat <- glm(cbind(D,Y) ~ Age + Per,
+ family=poisreg(link=log), data= tdk)
> round(ci.exp(mCat), 2)

exp(Est.) 2.5% 97.5%
(Intercept) 1.47 1.26 1.72
Age[20,25) 3.13 2.75 3.56
Age[25,30) 4.90 4.33 5.54
Age[30,35) 5.50 4.87 6.22
Age[35,40) 4.78 4.22 5.42
Age[40,45) 3.66 3.22 4.16
```

|                |      |      |      |
|----------------|------|------|------|
| Age[45,50)     | 2.60 | 2.27 | 2.97 |
| Age[50,55)     | 1.94 | 1.68 | 2.25 |
| Age[55,60)     | 1.47 | 1.25 | 1.72 |
| Age[60,65)     | 0.98 | 0.82 | 1.18 |
| Age[65,70)     | 0.92 | 0.76 | 1.12 |
| Age[70,75)     | 0.90 | 0.73 | 1.12 |
| Age[75,80]     | 0.86 | 0.67 | 1.11 |
| Per[1948,1953) | 1.12 | 0.96 | 1.30 |
| Per[1953,1958) | 1.30 | 1.13 | 1.50 |
| Per[1958,1963) | 1.53 | 1.33 | 1.76 |
| Per[1963,1968) | 1.68 | 1.47 | 1.92 |
| Per[1968,1973) | 1.98 | 1.74 | 2.25 |
| Per[1973,1978) | 2.33 | 2.05 | 2.64 |
| Per[1978,1983) | 2.66 | 2.35 | 3.01 |
| Per[1983,1988) | 2.83 | 2.50 | 3.20 |
| Per[1988,1993) | 3.08 | 2.73 | 3.47 |
| Per[1993,1998] | 3.31 | 2.93 | 3.74 |

What do the estimated rate ratios tell about the age and period effects?

16. A graphical inspection of point estimates and confidence intervals can be obtained as follows. In the beginning it is useful to define shorthands for the pertinent mid-age and mid-period values of the different intervals

```
> aMid <- seq(17.5, 77.5, by = 5)
> pMid <- seq(1945, 1995, by = 5)
> par(mfrow=c(1,2))
> plot(c(15,80), c(0.6, 6), type="n", log="y",
+ cex.lab = 1.5, cex.axis = 1.5,
+ xlab = "Age (years)", ylab = "Rate ratio")
> lines(aMid, c(1, ci.exp(mCat)[2:13, 1]), type = "o", pch = 16)
> segments(aMid[-1], ci.exp(mCat)[2:13, 2],
+ aMid[-1], ci.exp(mCat)[2:13, 3])
> plot(c(1943,1998), c(0.6, 6), type="n", log="y",
+ cex.lab = 1.5, cex.axis = 1.5,
+ xlab = "Calendar year - 1900", ylab = "Rate ratio")
> lines(pMid,c(1, ci.exp(mCat)[14:23, 1]), type = 'o', pch = 16)
> segments(pMid[-1], ci.exp(mCat)[14:23, 2],
+ pMid[-1], ci.exp(mCat)[14:23, 3])
```

17. In the fitted model the reference category for each factor was the first one. As age is the dominating factor, it may be more informative to remove the intercept from the model. As a consequence the age effects describe fitted rates at the reference level of the period factor. For the latter one could choose the middle period 1968-72.

```
> tdk$Per70 <- Relevel(tdk$Per, ref = 6)
> mCat2 <- glm(cbind(D,Y) ~ -1 + Age +Per70,
+ family=poisreg(link=log), data= tdk)
> round(ci.exp(mCat2), 2)
```

|            | exp(Est.) | 2.5%  | 97.5% |
|------------|-----------|-------|-------|
| Age[15,20) | 2.91      | 2.55  | 3.33  |
| Age[20,25) | 9.12      | 8.31  | 10.01 |
| Age[25,30) | 14.28     | 13.11 | 15.55 |
| Age[30,35) | 16.03     | 14.72 | 17.46 |
| Age[35,40) | 13.94     | 12.76 | 15.23 |

|                  |       |      |       |
|------------------|-------|------|-------|
| Age[40,45)       | 10.66 | 9.71 | 11.71 |
| Age[45,50)       | 7.57  | 6.83 | 8.39  |
| Age[50,55)       | 5.67  | 5.05 | 6.36  |
| Age[55,60)       | 4.28  | 3.75 | 4.88  |
| Age[60,65)       | 2.85  | 2.43 | 3.35  |
| Age[65,70)       | 2.68  | 2.25 | 3.19  |
| Age[70,75)       | 2.63  | 2.16 | 3.20  |
| Age[75,80]       | 2.51  | 1.98 | 3.18  |
| Per70[1943,1948) | 0.51  | 0.44 | 0.58  |
| Per70[1948,1953) | 0.57  | 0.50 | 0.64  |
| Per70[1953,1958) | 0.66  | 0.58 | 0.74  |
| Per70[1958,1963) | 0.77  | 0.69 | 0.87  |
| Per70[1963,1968) | 0.85  | 0.76 | 0.95  |
| Per70[1973,1978) | 1.18  | 1.07 | 1.30  |
| Per70[1978,1983) | 1.35  | 1.22 | 1.48  |
| Per70[1983,1988) | 1.43  | 1.30 | 1.57  |
| Per70[1988,1993) | 1.56  | 1.42 | 1.70  |
| Per70[1993,1998] | 1.67  | 1.53 | 1.84  |

We shall plot just the point estimates from the latter model

```
> par(mfrow=c(1,2))
> plot(c(15,80), c(2, 20), type="n", log="y", cex.lab = 1.5, cex.axis = 1.5,
+ xlab = "Age (years)", ylab = "Incidence rate (per 100000 y)")
> lines(aMid, c(ci.exp(mCat2)[1:13, 1]), type = "o", pch = 16)
> plot(c(1943,1998), c(0.4, 2), type="n", log="y",
+ cex.lab = 1.5, cex.axis = 1.5,
+ xlab = "Calendar year", ylab = "Rate ratio")
> lines(pMid, c(ci.exp(mCat2)[14:18, 1], 1, ci.exp(mCat2)[19:23, 1]),
+ type = "o", pch = 16)
> abline(h=1, col="gray")
```

### 2.10.7 Generalized additive model with penalized splines

It is obvious that the age effect on the log-rate scale is highly non-linear. Yet, it is less clear whether the true period effect deviates from linearity. Nevertheless, there are good indications to try fitting smooth continuous functions for both.

- As the next task we fit a generalized additive model for the log-rate on continuous age and period applying penalized splines with default settings of function `gam()` in package `mgcv`. In this fitting an “optimal” value for the penalty parameter is chosen based on an AIC-like criterion known as UBRE.

```
> library(mgcv)
> mPen <- gam(cbind(D, Y) ~ s(A) + s(P),
+ family = poisreg(link=log), data = tdk)
> summary(mPen)

Family: poisson
Link function: log

Formula:
cbind(D, Y) ~ s(A) + s(P)

Parametric coefficients:
```

```

 Estimate Std. Error z value Pr(>|z|)
(Intercept) 1.70960 0.01793 95.33 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 8.143 8.765 2560 <2e-16 ***
s(P) 3.046 3.790 1054 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.598 Deviance explained = 53.6%
UBRE = 0.082051 Scale est. = 1 n = 3510

```

The summary is quite brief, and the only estimated coefficient is the intercept, which sets the baseline level for the log-rates, against which the relative age effects and period effects will be contrasted. On the rate scale the baseline level 5.53 per 100000 y is obtained by `exp(1.7096)`.

19. See also the default plot for the fitted curves (solid lines) describing the age and the period effects which are interpreted as contrasts to the baseline level on the log-rate scale.

```

> par(mfrow=c(1,2))
> plot(mPen, seWithMean=TRUE)

```

The dashed lines describe the 95 % confidence band for the pertinent curve. One could get the impression that year 1968 would be some kind of reference value for the period effect, like period 1968-72 chosen as the reference in the categorical model previously fitted. This is not the case, however, because `gam()` by default parametrizes the spline effects such that the reference level, at which the spline effect is nominally zero, is the overall “grand mean” value of the log-rate in the data. This corresponds to the principle of *sum contrasts* (`contr.sum`) for categorical explanatory factors.

From the summary you will also find that the degrees of freedom value required for the age effect is nearly the same as the default dimension  $k - 1 = 9$  of the part of the model matrix (or basis) initially allocated for each smooth function. (Here  $k$  refers to the relevant argument that determines the basis dimension when specifying a smooth term by `s()` in the model formula). On the other hand the period effect takes just about 3 df.

20. It is a good idea to do some diagnostic checking of the fitted model

```

> par(mfrow=c(2,2))
> gam.check(mPen)

Method: UBRE Optimizer: outer newton
full convergence after 7 iterations.
Gradient range [-9.390731e-10,1.362468e-06]
(score 0.0820511 & scale 1).
Hessian positive definite, eigenvalue range [0.0002209238,0.0003824007].
Model rank = 19 / 19

```

Basis dimension (k) checking results. Low p-value (k-index<1) may

indicate that  $k$  is too low, especially if edf is close to  $k'$ .

```

 k' edf k-index p-value
s(A) 9.00 8.14 0.93 0.005 **
s(P) 9.00 3.05 0.95 0.100 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

The four diagnostic plots are analogous to some of those used in the context of linear models for Gaussian responses, but not all of them may be as easy to interpret. – Pay attention to the note given in the printed output about the value of  $k$ .

21. Let us refit the model but now with an increased  $k$  for age:

```

> mPen2 <- gam(cbind(D,Y) ~ s(A, k=20) + s(P),
+ family = poisreg(link=log), data = tdk)
> summary(mPen2)

Family: poisson
Link function: log

Formula:
cbind(D, Y) ~ s(A, k = 20) + s(P)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 1.70863 0.01795 95.17 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 11.132 13.406 2553 <2e-16 ***
s(P) 3.045 3.788 1054 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.599 Deviance explained = 53.7%
UBRE = 0.081809 Scale est. = 1 n = 3510

> par(mfrow=c(2,2))
> gam.check(mPen2)

Method: UBRE Optimizer: outer newton
full convergence after 6 iterations.
Gradient range [-2.397845e-12,2.90395e-09]
(score 0.08180917 & scale 1).
Hessian positive definite, eigenvalue range [0.00022158,0.0009322215].
Model rank = 29 / 29

Basis dimension (k) checking results. Low p-value (k-index<1) may
indicate that k is too low, especially if edf is close to k'.

 k' edf k-index p-value
s(A) 19.00 11.13 0.93 0.01 **
s(P) 9.00 3.05 0.95 0.13

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

With this choice of  $k$  the df value for age became about 11, which is well below  $k - 1 = 19$ . Let us plot the fitted curves from this fitting, too

```
> par(mfrow=c(1,2))
> plot(mPen2, seWithMean=TRUE)
> abline(v=1968, h=0, lty=3)
```

There does not seem to have happened any essential changes from the previously fitted curves, so maybe 8 df could, after all, be quite enough for the age effect.

22. Graphical presentation of the effects using `plot.gam()` can be improved. For instance, we may present the age effect to describe the “mean” incidence rates by age, averaged over the whole time span of 54 years. This is obtained by adding the estimated intercept to the estimated smooth curve for the age effect and showing the antilogarithms of the ordinates of the curve. For that purpose we need to extract the intercept and modify the labels of the  $y$ -axis accordingly. The estimated period curve can also be expressed in terms of relative incidence rates in relation to the fitted baseline rate, as determined by the model intercept.

```
> par(mfrow=c(1,2))
> icpt <- coef(mPen2)[1] # estimated intercept
> plot(mPen2, seWithMean=TRUE, select=1, rug=FALSE,
+ yaxt="n", ylim= c(log(1),log(20)) - icpt,
+ xlab="Age (y)", ylab="Mean rate (/100000 y)")
> axis(2, at = log(c(1, 2, 5, 10, 20)) - icpt, labels=c(1, 2, 5, 10, 20))
> plot(mPen2, seWithMean=TRUE, select=2, rug=FALSE,
+ yaxt="n", ylim=c(log(0.4), log(2)),
+ xlab="Calendar year", ylab="Relative rate")
> axis(2, at=log(c(0.5, 0.75, 1, 1.5, 2)), labels = c(0.5, 0.75, 1, 1.5, 2))
> abline(v=1968, h=0, lty=3)
```

One could continue the analysis of these data by fitting an age-cohort model as an alternative to the age-period model, as well as an age-cohort-period model.

### 2.10.8 Extra: Generalized additive model with natural regression splines

23. Instead of penalized splines one may use ordinary regression splines, in which the user specifies the model matrix (basis) by choosing a suitable number of knots and their locations. We prefer natural splines for the purpose. Fitting these models can be done with `glm()` such that in the model formula the spline components are defined by function `Ns()`

```
> mNs <- glm(cbind(D,Y) ~ Ns(A, knots = seq(15, 75, 10)) +
+ Ns(P, knots = seq(1950, 1990, 10)),
+ family=poisreg, data=tdk)
> summary(mNs)
```

Call:

```
glm(formula = cbind(D, Y) ~ Ns(A, knots = seq(15, 75, 10)) +
 Ns(P, knots = seq(1950, 1990, 10)), family = poisreg, data = tdk)
```

```

Coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.02223 0.07565 0.294 0.768821
Ns(A, knots = seq(15, 75, 10))1 2.14060 0.06984 30.649 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))2 1.65943 0.09958 16.665 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))3 0.92379 0.09965 9.271 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))4 -0.39445 0.10614 -3.716 0.000202 ***
Ns(A, knots = seq(15, 75, 10))5 2.41141 0.16930 14.244 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))6 -0.99257 0.07998 -12.410 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))1 0.53918 0.05905 9.131 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))2 0.80093 0.03957 20.239 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))3 1.20292 0.06627 18.152 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))4 0.83731 0.03477 24.080 < 2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for poisson family taken to be 1)

```

Null deviance: 8129.6 on 3509 degrees of freedom
Residual deviance: 3788.2 on 3499 degrees of freedom
AIC: 10837

```

Number of Fisher Scoring iterations: 6

Again, the summary provides not so interpretable quantities, so we need graphical presentation of the effects.

24. As in previous models we want to describe the age effect on the original rate scale merging the intercept. In the categorical model we chose the years 1968–72 as the reference period. Here we assign year 1970 as the reference date, so that the age curve describes the estimated age effect and the period curve describes the rate ratio versus the reference date. To this end we can utilize functions `ci.pred` to make predicted rates for the reference date, and `ci.exp` to extract predicted rate-ratios relative to the reference (see the help page for `ci.exp`).

What is needed are data frames with values for the covariates `A`, `P` and `Y`, one data frame for the predictions and two data frames representing the rate ratios we want:

```

> summary(mNs)

Call:
glm(formula = cbind(D, Y) ~ Ns(A, knots = seq(15, 75, 10)) +
 Ns(P, knots = seq(1950, 1990, 10)), family = poisreg, data = tdk)

Coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.02223 0.07565 0.294 0.768821
Ns(A, knots = seq(15, 75, 10))1 2.14060 0.06984 30.649 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))2 1.65943 0.09958 16.665 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))3 0.92379 0.09965 9.271 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))4 -0.39445 0.10614 -3.716 0.000202 ***
Ns(A, knots = seq(15, 75, 10))5 2.41141 0.16930 14.244 < 2e-16 ***
Ns(A, knots = seq(15, 75, 10))6 -0.99257 0.07998 -12.410 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))1 0.53918 0.05905 9.131 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))2 0.80093 0.03957 20.239 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))3 1.20292 0.06627 18.152 < 2e-16 ***
Ns(P, knots = seq(1950, 1990, 10))4 0.83731 0.03477 24.080 < 2e-16 ***

```

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for poisson family taken to be 1)

 Null deviance: 8129.6 on 3509 degrees of freedom
Residual deviance: 3788.2 on 3499 degrees of freedom
AIC: 10837

Number of Fisher Scoring iterations: 6

> aa <- 15:79
> pp <- 1943:1996
> # for the prediction
> ndp <- data.frame(A=aa, P=1970, Y=1)
> # for the RR between pp and 1970
> ndx <- data.frame(A=50, P=pp , Y=1)
> ndr <- data.frame(A=50, P=1970, Y=1)
> par(mfrow=c(1,2))
> matplot(aa, ci.pred(mNs, ndp),
+ log="y", xlab="Age", ylab="Incidence rate (per 100000 y)",
+ type="l", lty=1, lwd=c(3,1,1), col = c("red", "blue", "blue"))
> matplot(pp, ci.exp(mNs, list(ndx, ndr)),
+ log="y", xlab="Year", ylab="Rate ratio",
+ type="l", lty=1, lwd=c(3,1,1), col= c("red", "blue", "blue"))
> abline(h=1,v=1970)

```

Inspect the curves. Are they very different from those you got from the penalized splines model?

The nice thing about the approach is that exactly the same piece of code works for the gam model, so we can show the gam model with shades on top of the Ns results:

```

> par(mfrow=c(1,2))
> matplot(ndp$A, ci.pred(mNs, ndp),
+ log="y", xlab="Age", ylab="Incidence rate (per 100000 y)",
+ type="l", lty=1, lwd=c(3,1,1), col = c("red", "blue", "blue"))
> matshade(ndp$A, ci.pred(mPen2, ndp), lwd=2, lty=3)
> matplot(ndx$P, ci.exp(mNs, list(ndx, ndr)),
+ log="y", xlab="Year", ylab="Rate ratio",
+ type="l", lty=1, lwd=c(3,1,1), col= c("red", "blue", "blue"))
> matshade(ndx$P, ci.exp(mPen2, list(ndx, ndr)), lwd=2, lty=3)
> abline(h=1,v=1970)

```

One obvious difference is found in the way the error margins for the period effect are displayed. In the current model a specific reference calendar year, 1970, was chosen as a fixed reference point, and the rate ratio for all other calendar times describes a contrast of that time point versus year 1970. Therefore, there is no uncertainty in the rate ratio for 1970. In the penalized splines model no time point was explicitly chosen as a fixed reference, and the fitted period curve as well as its confidence band aims at estimating the period effect in relation to the baseline rate, and the uncertainty concerns the location of the whole curve.

25. Fit another spline model but now with greater numbers of knots. For instance, for age you may assign 13 knots from 15 to 75 years in steps of 5 years, and for period 11 knots from 45 to 95 years. Plot also the estimated age and period effects and comment the difference to our first spline model.



## 2.12 Survival analysis: Oral cancer patients

### 2.12.1 Description of the data

File `oralca2.txt`, that you may access from a url address to be given in the practical, contains data from 338 patients having an oral squamous cell carcinoma diagnosed and treated in one tertiary level oncological clinic in Finland since 1985, followed-up for mortality until 31 December 2008. The dataset contains the following variables:

```
sex = sex, a factor with categories 1 = "Female", 2 = "Male",
age = age (years) at the date of diagnosing the cancer,
stage = TNM stage of the tumour (factor): 1 = "I", ..., 4 = "IV", 5 = "unkn",
time = follow-up time (in years) since diagnosis until death or censoring,
event = event ending the follow-up (numeric):
 0 = censoring alive, 1 = death from oral cancer, 2 = death from other causes.
```

### 2.12.2 Loading the packages and the data

26. Load the R packages `Epi`, and `survival` needed in this exercise.

```
> library(Epi)
> library(survival)
```

27. Read the datafile `oralca2.txt` from a website, whose precise address will be given in the practical, into an R data frame named `orca`. Look at the head, structure and the summary of the data frame. Using function `table()` count the numbers of censorings as well as deaths from oral cancer and other causes, respectively, from the `event` variable.

```
> orca <- read.table("./data/oralca2.txt", header=T)
> head(orca) ; str(orca) ; summary(orca)
```

```
 sex age stage time event
1 Male 65.42274 unkn 5.081 0
2 Female 83.08783 III 0.419 1
3 Male 52.59008 II 7.915 2
4 Male 77.08630 I 2.480 2
5 Male 80.33622 IV 2.500 1
6 Female 82.58132 IV 0.167 2
```

```
'data.frame': 338 obs. of 5 variables:
 $ sex : chr "Male" "Female" "Male" "Male" ...
 $ age : num 65.4 83.1 52.6 77.1 80.3 ...
 $ stage: chr "unkn" "III" "II" "I" ...
 $ time : num 5.081 0.419 7.915 2.48 2.5 ...
 $ event: int 0 1 2 2 1 2 0 1 1 0 ...
```

```
 sex age stage time
Length:338 Min. :15.15 Length:338 Min. : 0.085
Class :character 1st Qu.:53.24 Class :character 1st Qu.: 1.333
Mode :character Median :64.86 Mode :character Median : 3.869
 Mean :63.51 Mean : 5.662
 3rd Qu.:74.29 3rd Qu.: 8.417
 Max. :92.24 Max. :23.258

 event
Min. :0.0000
```

```
1st Qu.:0.0000
Median :1.0000
Mean :0.9941
3rd Qu.:2.0000
Max. :2.0000
```

### 2.12.3 Total mortality: Kaplan–Meier analyses

1. We start our analysis of total mortality pooling the two causes of death into a single outcome. First, construct a *survival object* `orca$suob` from the event variable and the follow-up time using function `Surv()`. Look at the structure and summary of `orca$suob`.

```
> orca$suob <- Surv(orca$time, 1*(orca$event > 0))
> str(orca$suob)

'Surv' num [1:338, 1:2] 5.081+ 0.419 7.915 2.480 2.500 0.167 5.925+ 1.503 1.503 1.503 ...
- attr(*, "dimnames")=List of 2
..$: NULL
..$: chr [1:2] "time" "status"
- attr(*, "type")= chr "right"

> summary(orca$suob)

 time status
Min. : 0.085 Min. :0.0000
1st Qu.: 1.333 1st Qu.:0.0000
Median : 3.869 Median :1.0000
Mean : 5.662 Mean :0.6775
3rd Qu.: 8.417 3rd Qu.:1.0000
Max. :23.258 Max. :1.0000
```

2. Create a `survfit` object `s.all`, which does the default calculations for a Kaplan–Meier analysis of the overall (marginal) survival curve.

```
> s.all <- survfit(suob ~ 1, data=orca)
```

See the structure of this object and apply `print()` method on it, too. Look at the results; what do you find?

```
> s.all

Call: survfit(formula = suob ~ 1, data = orca)

 n events median 0.95LCL 0.95UCL
[1,] 338 229 5.42 4.33 6.92

> str(s.all)

List of 16
 $ n : int 338
 $ time : num [1:251] 0.085 0.162 0.167 0.17 0.246 0.249 0.252 0.329 0.334 0.413 ...
 $ n.risk : num [1:251] 338 336 334 330 328 327 326 323 322 321 ...
 $ n.event : num [1:251] 2 2 4 2 1 1 3 1 1 1 ...
 $ n.censor : num [1:251] 0 0 0 0 0 0 0 0 0 0 ...
```

```

$ surv : num [1:251] 0.994 0.988 0.976 0.97 0.967 ...
$ std.err : num [1:251] 0.0042 0.00595 0.00847 0.0095 0.00998 ...
$ cumhaz : num [1:251] 0.00592 0.01187 0.02385 0.02991 0.03295 ...
$ std.chaz : num [1:251] 0.00418 0.00593 0.00843 0.00946 0.00994 ...
$ type : chr "right"
$ logse : logi TRUE
$ conf.int : num 0.95
$ conf.type : chr "log"
$ lower : num [1:251] 0.986 0.977 0.96 0.953 0.949 ...
$ upper : num [1:251] 1 1 0.993 0.989 0.987 ...
$ call : language survfit(formula = suob ~ 1, data = orca)
- attr(*, "class")= chr "survfit"

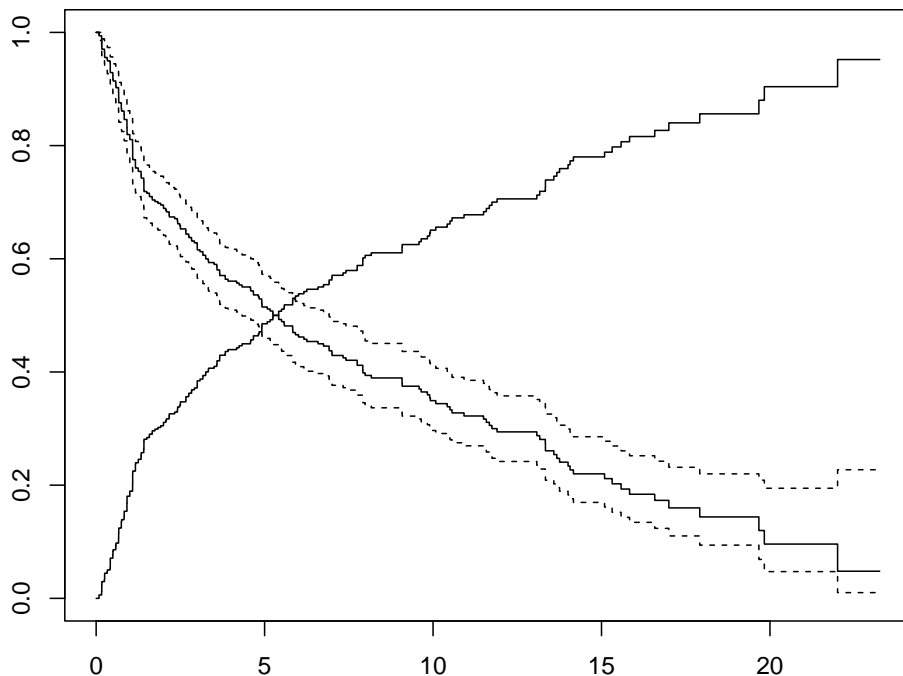
```

3. The `summary` method for a `survfit` object would return a lengthy life table. However, the `plot` method with default arguments offers the Kaplan–Meier curve for a conventional illustration of the survival experience in the whole patient group. Alternatively, instead of graphing survival proportions, one can draw a curve describing their complements: the cumulative mortality proportions. This curve is drawn together with the survival curve as the result of the second command line below.

```

> plot(s.all)
> lines(s.all, fun = "event", mark.time=F, conf.int=F)

```



The effect of option `mark.time=F` is to omit marking the times when censorings occurred.

### 2.12.4 Total mortality by stage

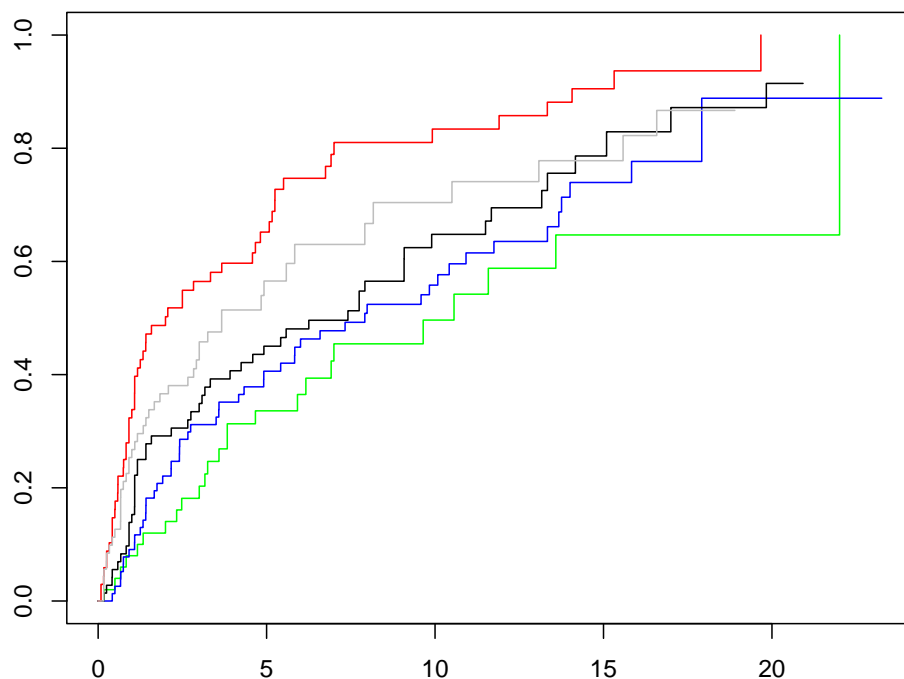
Tumour stage is an important prognostic factor in cancer survival studies.

1. Plot separate cumulative mortality curves for the different stage groups marking them with different colours, the order which you may define yourself. Also find the median survival time for each stage.

```
> s.stg <- survfit(suob ~ stage, data= orca)
> col5 <- c("green", "blue", "black", "red", "gray")
> plot(s.stg, col= col5, fun="event", mark.time=F)
> s.stg
```

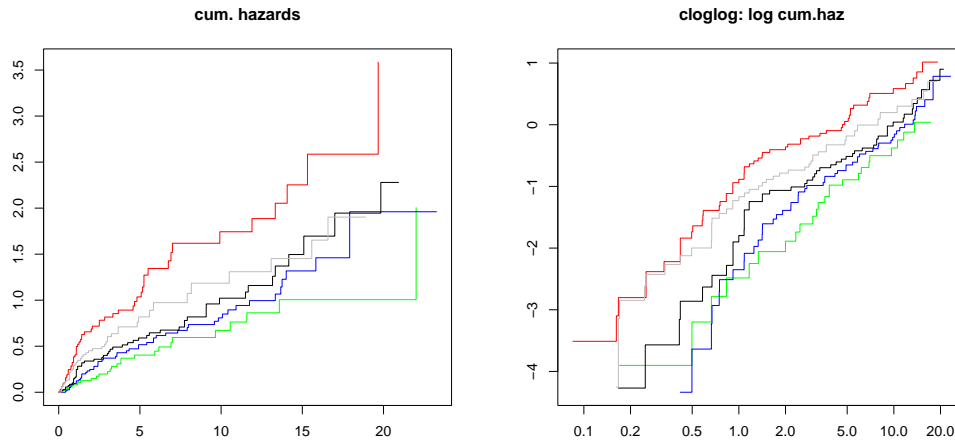
```
Call: survfit(formula = suob ~ stage, data = orca)
```

|            | n  | events | median | 0.95LCL | 0.95UCL |
|------------|----|--------|--------|---------|---------|
| stage=I    | 50 | 25     | 10.56  | 6.17    | NA      |
| stage=II   | 77 | 51     | 7.92   | 4.92    | 13.34   |
| stage=III  | 72 | 51     | 7.41   | 3.92    | 9.90    |
| stage=IV   | 68 | 57     | 2.00   | 1.08    | 4.82    |
| stage=unkn | 71 | 45     | 3.67   | 2.83    | 8.17    |



2. Create now two parallel plots of which the first one describes the cumulative hazards and the second one graphs the log-cumulative hazards against log-time for the different stages. Compare the two presentations with each other and with the one in the previous item.

```
> par(mfrow=c(1,2))
> plot(s.stg, col= col5, fun="cumhaz", main="cum. hazards")
> plot(s.stg, col= col5, fun="cloglog", main = "cloglog: log cum.haz")
```



3. If the survival times were *exponentially* distributed in a given (sub)population the corresponding cloglog-curve should follow an approximately linear pattern. Could this be the case here in the different stages?
4. Also, if the survival distributions of the different subpopulations would obey the *proportional hazards* model, the vertical distance between the cloglog-curves should be approximately constant over the time axis. Do these curves indicate serious deviation from the proportional hazards assumption?
5. In the lecture handouts (p. 34, 37) it was observed that the crude contrast between males and females in total mortality appears unclear, but the age-adjustment in the Cox model provided a more expected hazard ratio estimate. We shall examine the confounding by age somewhat closer. First categorize the continuous age variable into, say, three categories by function `cut()` using suitable breakpoints, like 55 and 75 years, and cross-tabulate sex and age group:

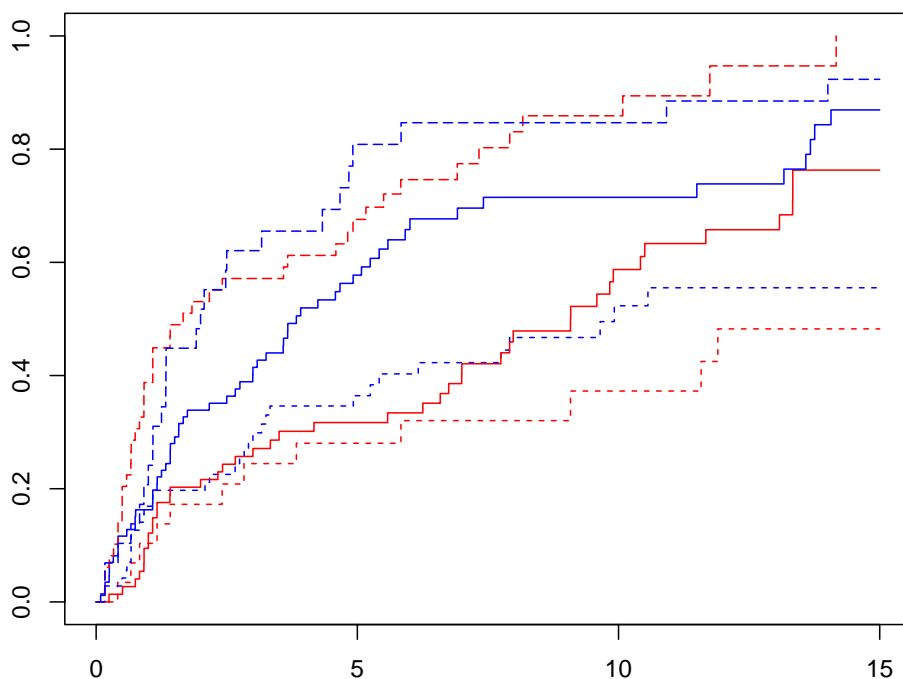
```
> orca$agegr <- cut(orca$age, br=c(0,55,75, 95))
> stat.table(list(sex, agegr), list(count(), percent(agegr)),
+ margins=T, data = orca)
```

| sex    | -----agegr----- |             |            | Total        |
|--------|-----------------|-------------|------------|--------------|
|        | (0,55]          | (55,75]     | (75,95]    |              |
| Female | 29<br>19.1      | 74<br>48.7  | 49<br>32.2 | 152<br>100.0 |
| Male   | 71<br>38.2      | 86<br>46.2  | 29<br>15.6 | 186<br>100.0 |
| Total  | 100<br>29.6     | 160<br>47.3 | 78<br>23.1 | 338<br>100.0 |

Male patients are clearly younger than females in these data.

Now, plot Kaplan–Meier curves jointly classified by sex and age.

```
> s.agrx <- survfit(suob ~ agegr + sex, data=orca)
> par(mfrow=c(1,1))
> plot(s.agrx, fun="event", mark.time=F, xlim = c(0,15),
+ col=rep(c("red", "blue"),3), lty=c(2,2, 1,1, 5,5))
```



In each ageband the mortality curve for males is on a higher level than that for females.

### 2.12.5 Event-specific cumulative mortality curves

We move on to analysing cumulative mortalities for the two causes of death separately, first overall and then by prognostic factors.

1. Use the `survfit`-function in `survival` package with option `type="mstate"`.

```
> cif1 <- survfit(Surv(time, event, type="mstate") ~ 1,
+ data = orca)
> str(cif1)
```

List of 19

```
$ n : int 338
$ time : num [1:251] 0.085 0.162 0.167 0.17 0.246 0.249 0.252 0.329 0.334 0.413 ...
$ n.risk : int [1:251, 1:3] 338 336 334 330 328 327 326 323 322 321 ...
$ n.event : int [1:251, 1:3] 0 0 0 0 0 0 0 0 0 0 ...
```

```

$ n.censor : int [1:251] 0 0 0 0 0 0 0 0 0 0 ...
$ pstate : num [1:251, 1:3] 0.994 0.988 0.976 0.97 0.967 ...
$ p0 : num [1:3(1d)] 1 0 0
..- attr(*, "dimnames")=List of 1
.. ..$: chr [1:3] "(s0)" "1" "2"
$ cumhaz : num [1:251, 1:2] 0.00592 0.01187 0.01786 0.02089 0.02394 ...
..- attr(*, "dimnames")=List of 2
.. ..$: NULL
.. ..$: chr [1:2] "1.2" "1.3"
$ std.err : num [1:251, 1:3] 0.00417 0.00588 0.00827 0.00922 0.00965 ...
$ sp0 : num [1:3] 0 0 0
$ logse : logi FALSE
$ transitions: 'table' int [1:3, 1:3] 122 0 0 107 0 0 109 0 0
..- attr(*, "dimnames")=List of 2
.. ..$ from: chr [1:3] "(s0)" "1" "2"
.. ..$ to : chr [1:3] "1" "2" "(censored)"
$ lower : num [1:251, 1:3] 0.986 0.977 0.96 0.953 0.949 ...
$ upper : num [1:251, 1:3] 1 1 0.993 0.989 0.987 ...
$ conf.type : chr "log"
$ conf.int : num 0.95
$ states : chr [1:3] "(s0)" "1" "2"
$ type : chr "mright"
$ call : language survfit(formula = Surv(time, event, type = "mstate") ~ 1, data =
- attr(*, "class")= chr [1:2] "survfitms" "survfit"

```

- One could apply here the plot method of the survfit object to plot the cumulative incidences for each cause. However, we suggest that you use instead a simple function `plotCIF()` found in the `Epi` package. The main arguments are

`data` = data frame created by function `survfit()`, (2.1)

`event` = indicator for the event: values 1 or 2. (2.2)

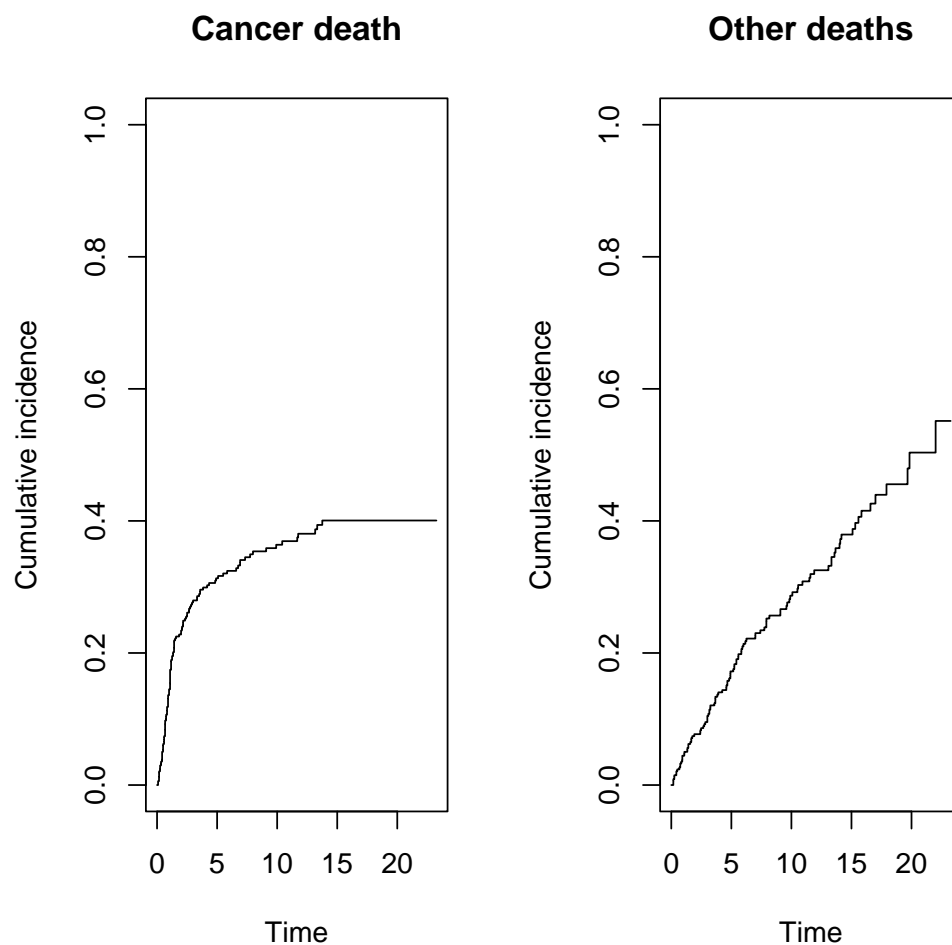
Other arguments are like in the ordinary `plot()` function.

- Draw two parallel plots describing the overall cumulative incidence curves for both causes of death

```

> par(mfrow=c(1,2))
> plotCIF(cif1, 1, main = "Cancer death")
> plotCIF(cif1, 2, main= "Other deaths")

```



4. Compute the estimated cumulative incidences by stage for both causes of death. Now you have to add variable `stage` to `survfit`-function.

See the structure of the resulting object, in which you should observe `strata` variable containing the stage grouping variable. Plot the pertinent curves in two parallel graphs. Cut the *y*-axis for a more efficient graphical presentation

```
> col5 <- c("green", "blue", "black", "red", "gray")
> cif2 <- survfit(Surv(time, event, type="mstate") ~ stage,
+ data = orca)
> str(cif2)

List of 20
 $ n : int [1:5] 50 77 72 68 71
 $ time : num [1:307] 0.17 0.498 0.665 0.832 1.166 ...
 $ n.risk : int [1:307, 1:3] 50 49 48 47 46 45 44 43 42 41 ...
 $ n.event : int [1:307, 1:3] 0 0 0 0 0 0 0 0 0 0 ...
 $ n.censor : int [1:307] 0 0 0 0 0 0 1 0 0 0 ...
 $ pstate : num [1:307, 1:3] 0.98 0.96 0.94 0.92 0.9 ...
 $ p0 : num [1:5, 1:3] 1 1 1 1 1 0 0 0 0 0 ...
 .. attr(*, "dimnames")=List of 2
$: chr [1:5] "stage=I" "stage=II" "stage=III" "stage=IV" ...
$: chr [1:3] "(s0)" "1" "2"
 $ strata : Named int [1:5] 49 75 62 58 63
```

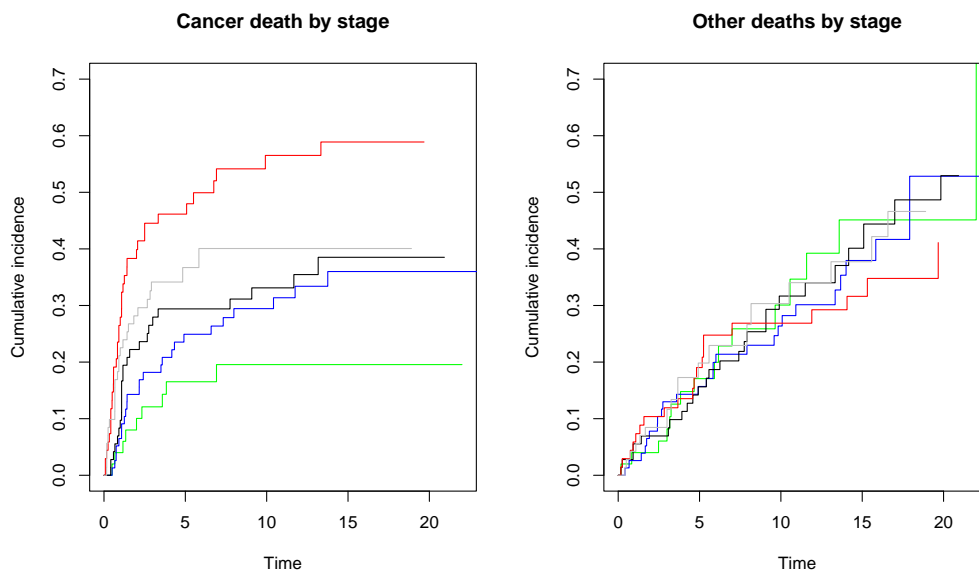


```

..- attr(*, "names")= chr [1:5] "stage=I" "stage=II" "stage=III" "stage=IV" ...
$ std.err : num [1:307, 1:3] 0.0198 0.0277 0.0336 0.0384 0.0424 ...
$ sp0 : num [1:5, 1:3] 0 0 0 0 0 0 0 0 0 0 ...
$ logse : logi FALSE
$ cumhaz : num [1:307, 1:2] 0 0.0204 0.0412 0.0412 0.063 ...
..- attr(*, "dimnames")=List of 2
.. ..$: NULL
.. ..$: chr [1:2] "1.2" "1.3"
$ transitions: 'table' int [1:3, 1:3] 122 0 0 107 0 0 109 0 0
..- attr(*, "dimnames")=List of 2
.. ..$ from: chr [1:3] "(s0)" "1" "2"
.. ..$ to : chr [1:3] "1" "2" "(censored)"
$ lower : num [1:307, 1:3] 0.942 0.907 0.876 0.848 0.821 ...
$ upper : num [1:307, 1:3] 1 1 1 0.998 0.987 ...
$ conf.type : chr "log"
$ conf.int : num 0.95
$ states : chr [1:3] "(s0)" "1" "2"
$ type : chr "mright"
$ call : language survfit(formula = Surv(time, event, type = "mstate") ~ stage, dat
- attr(*, "class")= chr [1:2] "survfitms" "survfit"

> par(mfrow=c(1,2))
> plotCIF(cif2, 1, main = "Cancer death by stage",
+ col = col5, ylim = c(0, 0.7))
> plotCIF(cif2, 2, main= "Other deaths by stage",
+ col=col5, ylim = c(0, 0.7))

```

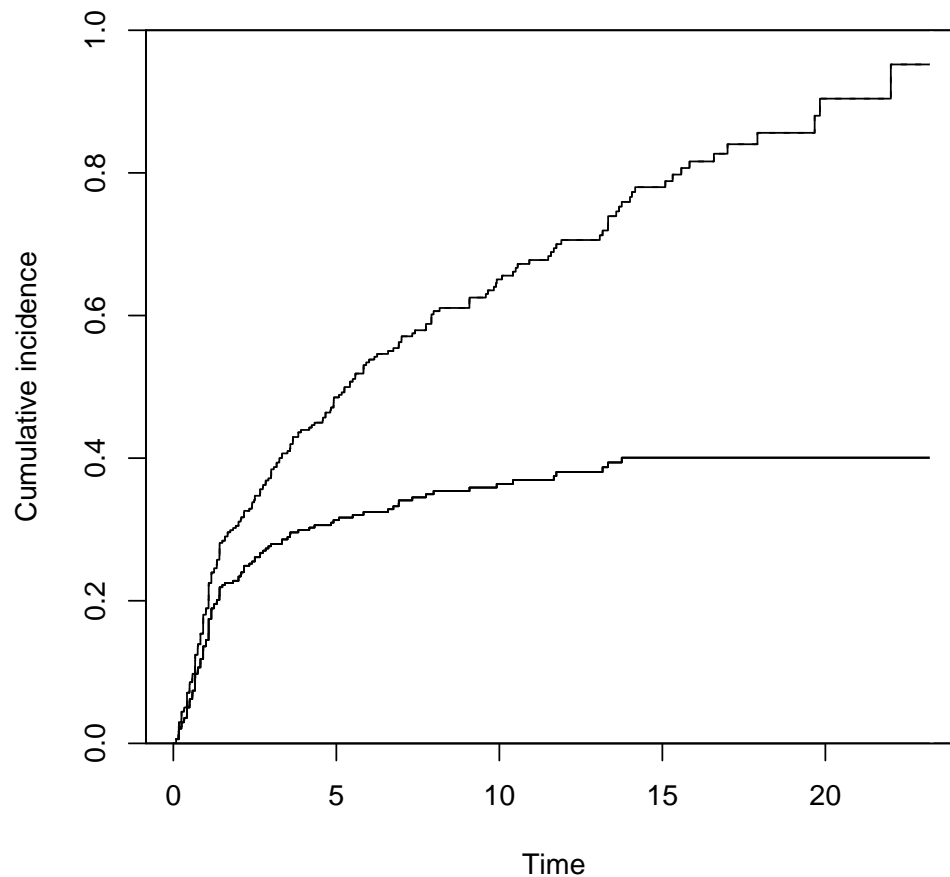


Compare the two plots. What would you conclude about the effect of stage on the two causes of death

?

- Using another function `stackedCIF()` in Epi you can put the two cumulative incidence curves in one graph but stacked upon one another such that the lower curve is for the cancer deaths and the upper curve is for total mortality, and the vertical difference between the two curves describes the cumulative mortality from other causes. You can also add some colours for the different zones:

```
> par(mfrow=c(1,1))
> stackedCIF(cif1,colour = c("gray70", "gray85"))
```



### 2.12.6 Regression modelling of overall mortality.

1. Fit the semiparametric proportional hazards regression model, a.k.a. the Cox model, on all deaths including sex, age and stage as covariates. Use function `coxph()` in package `survival`. It is often useful to center and scale continuous covariates like `age` here. The estimated rate ratios and their confidence intervals can also here be displayed by applying `ci.lin()` on the fitted model object.

```
> options(show.signif.stars = F)
> m1 <- coxph(suob ~ sex + I((age-65)/10) + stage, data= orca)
> summary(m1)
```

Call:

```
coxph(formula = suob ~ sex + I((age - 65)/10) + stage, data = orca)
```

```
n= 338, number of events= 229
```

|         | coef    | exp(coef) | se(coef) | z     | Pr(> z ) |
|---------|---------|-----------|----------|-------|----------|
| sexMale | 0.35139 | 1.42104   | 0.14139  | 2.485 | 0.012947 |

```

I((age - 65)/10) 0.41603 1.51593 0.05641 7.375 1.65e-13
stageII 0.03492 1.03554 0.24667 0.142 0.887421
stageIII 0.34545 1.41262 0.24568 1.406 0.159708
stageIV 0.88542 2.42399 0.24273 3.648 0.000265
stageunkn 0.58441 1.79393 0.25125 2.326 0.020016

```

```

 exp(coef) exp(-coef) lower .95 upper .95
sexMale 1.421 0.7037 1.0771 1.875
I((age - 65)/10) 1.516 0.6597 1.3573 1.693
stageII 1.036 0.9657 0.6386 1.679
stageIII 1.413 0.7079 0.8728 2.286
stageIV 2.424 0.4125 1.5063 3.901
stageunkn 1.794 0.5574 1.0963 2.935

```

```

Concordance= 0.674 (se = 0.02)
Likelihood ratio test= 86.76 on 6 df, p=<2e-16
Wald test = 80.5 on 6 df, p=3e-15
Score (logrank) test = 82.86 on 6 df, p=9e-16

```

```
> round(ci.exp(m1), 4)
```

```

 exp(Est.) 2.5% 97.5%
sexMale 1.4210 1.0771 1.8748
I((age - 65)/10) 1.5159 1.3573 1.6932
stageII 1.0355 0.6386 1.6793
stageIII 1.4126 0.8728 2.2864
stageIV 2.4240 1.5063 3.9007
stageunkn 1.7939 1.0963 2.9354

```

Look at the results. What are the main findings?

2. Check whether the data are sufficiently consistent with the assumption of proportional hazards with respect to each of the variables separately as well as globally, using the `cox.zph()` function.

```
> cox.zph(m1)
```

```

 chisq df p
sex 0.275 1 0.60
I((age - 65)/10) 1.706 1 0.19
stage 3.648 4 0.46
GLOBAL 5.144 6 0.53

```

3. No evidence against proportionality assumption could apparently be found. Moreover, no difference can be observed between stages I and II in the estimates. On the other hand, the group with stage unknown is a complex mixture of patients from various true stages. Therefore, it may be prudent to exclude these subjects from the data and to pool the first two stage groups into one. After that fit a model in the reduced data with the new stage variable.

```

> orca2 <- subset(orca, stage != "unkn")
> orca2$st3 <- Relevel(orca2$stage, list(1:2, 3, 4:5))

```

```

WARNING: orca2$stage has been converted to a factor with levels:
 I II III IV

```

```
> levels(orca2$st3) = c("I-II", "III", "IV")
> m2 <- update(m1, . ~ . - stage + st3, data=orca2)
> round(ci.exp(m2), 4)
```

|                  | exp(Est.) | 2.5%   | 97.5%  |
|------------------|-----------|--------|--------|
| sexMale          | 1.3284    | 0.9763 | 1.8074 |
| I((age - 65)/10) | 1.4637    | 1.2959 | 1.6534 |
| st3III           | 1.3657    | 0.9547 | 1.9536 |
| st3IV            | 2.3900    | 1.6841 | 3.3919 |

- Plot the predicted cumulative mortality curves by stage, jointly stratified by sex and age, focusing only on 40 and 80 year old patients, respectively, based on the fitted model m2. You need to create a new artificial data frame containing the desired values for the covariates.

```
> newd <- data.frame(sex = c(rep("Male", 6), rep("Female", 6)),
+ age = rep(c(rep(40, 3), rep(80, 3)), 2),
+ st3 = rep(levels(orca2$st3), 4))
> newd
```

|    | sex    | age | st3  |
|----|--------|-----|------|
| 1  | Male   | 40  | I-II |
| 2  | Male   | 40  | III  |
| 3  | Male   | 40  | IV   |
| 4  | Male   | 80  | I-II |
| 5  | Male   | 80  | III  |
| 6  | Male   | 80  | IV   |
| 7  | Female | 40  | I-II |
| 8  | Female | 40  | III  |
| 9  | Female | 40  | IV   |
| 10 | Female | 80  | I-II |
| 11 | Female | 80  | III  |
| 12 | Female | 80  | IV   |

```
> col3 <- c("green", "black", "red")
> par(mfrow=c(1,2))
> plot(survfit(m2, newdata= subset(newd, sex=="Male" & age==40)),
+ col=col3, fun="event", mark.time=F)
> lines(survfit(m2, newdata= subset(newd, sex=="Female" & age==40)),
+ col= col3, fun="event", lty = 2, mark.time=F)
> plot(survfit(m2, newdata= subset(newd, sex=="Male" & age==80)),
+ ylim = c(0,1), col= col3, fun="event", mark.time=F)
> lines(survfit(m2, newdata= subset(newd, sex=="Female" & age==80)),
+ col=col3, fun="event", lty=2, mark.time=F)
>
```

### 2.12.7 Modelling event-specific hazards and hazards of the subdistribution

- Fit the Cox model for the cause-specific hazard of cancer deaths with the same covariates as above. In this case only cancer deaths are counted as events and deaths from other causes are included into censorings.

```
> m2haz1 <- coxph(Surv(time, event==1) ~ sex + I((age-65)/10) + st3 , data=orca2)
> round(ci.exp(m2haz1), 4)
```

```

 exp(Est.) 2.5% 97.5%
sexMale 1.0171 0.6644 1.5569
I((age - 65)/10) 1.4261 1.2038 1.6893
st3III 1.5140 0.9012 2.5434
st3IV 3.1813 1.9853 5.0978

```

```
> cox.zph(m2haz1)
```

```

 chisq df p
sex 0.0724 1 0.788
I((age - 65)/10) 5.7620 1 0.016
st3 3.4195 2 0.181
GLOBAL 9.1216 4 0.058

```

Compare the results with those of model m2. What are the major differences?

2. Fit a similar model for deaths from other causes and compare the results.

```

> m2haz2 <- coxph(Surv(time, event==2) ~ sex + I((age-65)/10) + st3 , data=orca2)
> round(ci.exp(m2haz2), 4)

```

```

 exp(Est.) 2.5% 97.5%
sexMale 1.8103 1.1528 2.8431
I((age - 65)/10) 1.4876 1.2491 1.7715
st3III 1.2300 0.7488 2.0206
st3IV 1.6407 0.9522 2.8270

```

```
> cox.zph(m2haz2)
```

```

 chisq df p
sex 0.4071 1 0.52
I((age - 65)/10) 0.2435 1 0.62
st3 0.0443 2 0.98
GLOBAL 0.6444 4 0.96

```

3. Finally, fit the Fine–Gray model for the hazard of the subdistribution for cancer deaths with the same covariates as above. For this you have to first load package `cmprsk`, containing the necessary function `crr()`, and attach the data frame.

```

> library(cmprsk)
> attach(orca2)
> m2fg1 <- crr(time, event, cov1 = model.matrix(m2), failcode=1)
> summary(m2fg1, Exp=T)

```

Competing Risks Regression

Call:

```
crr(ftime = time, fstatus = event, cov1 = model.matrix(m2), failcode = 1)
```

```

 coef exp(coef) se(coef) z p-value
sexMale -0.0808 0.922 0.2118 -0.381 7.0e-01
I((age - 65)/10) 0.2791 1.322 0.0918 3.039 2.4e-03
st3III 0.3739 1.453 0.2588 1.445 1.5e-01
st3IV 1.0346 2.814 0.2327 4.446 8.8e-06

```

```

 exp(coef) exp(-coef) 2.5% 97.5%
sexMale 0.922 1.084 0.609 1.40
I((age - 65)/10) 1.322 0.756 1.104 1.58

```

```
st3III 1.453 0.688 0.875 2.41
st3IV 2.814 0.355 1.783 4.44
```

```
Num. cases = 267
Pseudo Log-likelihood = -493
Pseudo likelihood ratio test = 32.1 on 4 df,
```

Compare the results with those of model `m2` and `m2haz1`.

4. Fit a similar model for deaths from other causes and compare the results.

```
> m2fg2 <- crr(time, event, cov1 = model.matrix(m2), failcode=2)
> summary(m2fg2, Exp=T)
```

Competing Risks Regression

Call:

```
crr(ftime = time, fstatus = event, cov1 = model.matrix(m2), failcode = 2)
```

|                  | coef   | exp(coef) | se(coef) | z      | p-value |
|------------------|--------|-----------|----------|--------|---------|
| sexMale          | 0.558  | 1.748     | 0.2264   | 2.467  | 0.014   |
| I((age - 65)/10) | 0.187  | 1.205     | 0.0775   | 2.412  | 0.016   |
| st3III           | 0.086  | 1.090     | 0.2428   | 0.354  | 0.720   |
| st3IV            | -0.225 | 0.799     | 0.2795   | -0.803 | 0.420   |

|                  | exp(coef) | exp(-coef) | 2.5%  | 97.5% |
|------------------|-----------|------------|-------|-------|
| sexMale          | 1.748     | 0.572      | 1.122 | 2.72  |
| I((age - 65)/10) | 1.205     | 0.830      | 1.036 | 1.40  |
| st3III           | 1.090     | 0.918      | 0.677 | 1.75  |
| st3IV            | 0.799     | 1.252      | 0.462 | 1.38  |

```
Num. cases = 267
Pseudo Log-likelihood = -438
Pseudo likelihood ratio test = 9.43 on 4 df,
```

### 2.12.8 Lexis object with multi-state set-up

Before entering to analyses of cause-specific mortality it might be instructive to apply some Lexis tools to illustrate the competing-risks set-up. More detailed explanation of these tools will be given by Bendix in this afternoon.

1. Form a Lexis object from the data frame and print a summary of it. We shall name the main (and only) time axis in this object as `stime`.

```
> orca.lex <- Lexis(exit = list(stime = time),
+ exit.status = factor(event,
+ labels = c("Alive", "Oral ca. death", "Other death")),
+ data = orca)
```

```
NOTE: entry.status has been set to "Alive" for all.
NOTE: entry is assumed to be 0 on the stime timescale.
```

```
> summary(orca.lex)
```

```

Transitions:
 To
From Alive Oral ca. death Other death Records: Events: Risk time:
 Alive 109 122 107 338 229 1913.67

Transitions:
 To
From Persons:
 Alive 338

```

2. Draw a box diagram of the two-state set-up of competing transitions. Run first the following command line

```
boxes(orca.lex)
```

Now, move the cursor to the point in the graphics window, at which you wish to put the box for “Alive”, and click. Next, move the cursor to the point at which you wish to have the box for “Oral ca. death”, and click. Finally, do the same with the box for “Other death”. If you are not happy with the outcome, run the command line again and repeat the necessary mouse moves and clicks.

### 2.12.9 Poisson regression as an alternative to Cox model

It can be shown that the Cox model with an unspecified form for the baseline hazard  $\lambda_0(t)$  is mathematically equivalent to the following kind of Poisson regression model. Time is treated as a categorical factor with a dense division of the time axis into disjoint intervals or *timebands* such that only one outcome event occurs in each timeband. The model formula contains this time factor plus the desired explanatory terms.

A sufficient division of time axis is obtained by first setting the break points between adjacent timebands to be those time points at which an outcome event has been observed to occur. Then, the pertinent `lexis` object is created and after that it will be split according to those breakpoints. Finally, the Poisson regression model is fitted on the splitted `lexis` object using function `glm()` with appropriate specifications.

We shall now demonstrate the numerical equivalence of the Cox model `m2haz1` for oral cancer mortality that was fitted above, and the corresponding Poisson regression.

1. First we form the necessary `lexis` object by just taking the relevant subset of the already available `orca.lex` object. Upon that the three-level stage factor `st3` is created as above.

```

> orca2.lex <- subset(orca.lex, stage != "unkn")
> orca2.lex$st3 <- Relevel(orca2$stage, list(1:2, 3, 4:5))

WARNING: orca2$stage has been converted to a factor with levels:
 I II III IV

> levels(orca2.lex$st3) = c("I-II", "III", "IV")

```

Then, the break points of time axis are taken from the sorted event times, and the `lexis` object is split by those breakpoints. The `timeband` factor is defined according to the splitted survival times stored in variable `stime`.

```
> cuts <- sort(orca2$time[orca2$event==1])
> orca2.spl <- splitLexis(orca2.lex, br = cuts, time.scale="stime")
> orca2.spl$timeband <- as.factor(orca2.spl$time)
```

As a result we now have an expanded `lexis` object in which each subject has several rows; as many rows as there are such timebands during which he/she is still at risk. The outcome status `lex.Xst` has value 0 in all those timebands, over which the subject stays alive, but assumes the value 1 or 2 at his/her last interval ending at the time of death. – See now the structure of the splitted object.

```
> str(orca2.spl)

Classes 'Lexis' and 'data.frame': 12637 obs. of 14 variables:
 $ lex.id : int 2 2 2 2 2 2 3 3 3 3 ...
 $ stime : num 0 0.085 0.162 0.252 0.329 0.413 0 0.085 0.162 0.252 ...
 $ lex.dur : num 0.085 0.077 0.09 0.077 0.084 0.006 0.085 0.077 0.09 0.077 ...
 $ lex.Cst : Factor w/ 3 levels "Alive","Oral ca. death",...: 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst : Factor w/ 3 levels "Alive","Oral ca. death",...: 1 1 1 1 1 2 1 1 1 1 ...
 $ sex : chr "Female" "Female" "Female" "Female" ...
 $ age : num 83.1 83.1 83.1 83.1 83.1 ...
 $ stage : chr "III" "III" "III" "III" ...
 $ time : num 0.419 0.419 0.419 0.419 0.419 ...
 $ event : int 1 1 1 1 1 1 2 2 2 2 ...
 $ suob : 'Surv' num [1:12637, 1:2] 0.419 0.419 0.419 0.419 0.419 0.419 7.915 7
 .. attr(*, "dimnames")=List of 2
$: NULL
$: chr [1:2] "time" "status"
 ..- attr(*, "type")= chr "right"
 $ agegr : Factor w/ 3 levels "(0,55]","(55,75]",">75": 3 3 3 3 3 3 1 1 1 1 ...
 $ st3 : Factor w/ 3 levels "I-II","III","IV": 2 2 2 2 2 2 1 1 1 1 ...
 $ timeband : Factor w/ 72 levels "0","0.085","0.162",...: 1 2 3 4 5 6 1 2 3 4 ...
 - attr(*, "breaks")=List of 1
 ..$ stime: num [1:71] 0.085 0.162 0.252 0.329 0.413 0.419 0.496 0.498 0.504 0.58 ...
 - attr(*, "time.scales")= chr "stime"
 - attr(*, "time.since")= chr ""

> #orca2.spl[1:20,]
```

2. We are ready to fit the desired Poisson model for oral cancer death as the outcome. The splitted person-years are contained in `lex.dur`, and the explanatory variables are the same as in model `m2haz1`. – This fitting may take some time ...

```
> m2pois1 <- glm(1*(lex.Xst=="Oral ca. death") ~
+ -1 + timeband + sex + I((age-65)/10) + st3,
+ family=poisson, offset = log(lex.dur), data = orca2.spl)
```

We shall display the estimation results graphically for the baseline hazard (per 1000 person-years) and numerically for the rate ratios associated with the covariates. Before doing that it is useful to count the length `ntb` of the block occupied by baseline hazard in the whole vector of estimated parameters. However, owing to how the splitting to timebands was done, the last regression coefficient is necessarily zero and better be omitted when displaying the results. Also, as each timeband is quantitatively named according to its leftmost point, it is good to compute the midpoint values `tbmid` for the timebands

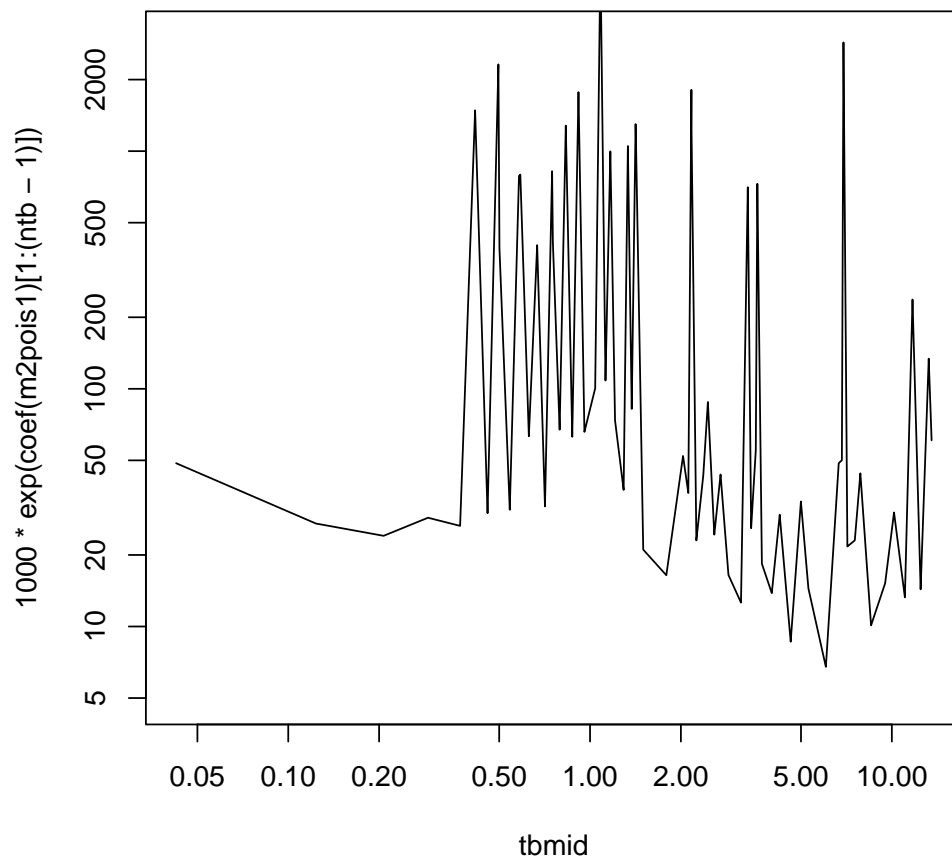


```
> tb <- as.numeric(levels(orca2.spl$timeband)) ; ntb <- length(tb)
> tbmid <- (tb[-ntb] + tb[-1])/2 # midpoints of the intervals
> round(ci.exp(m2poisl), 3)
```

|               | exp(Est.) | 2.5%  | 97.5%  |
|---------------|-----------|-------|--------|
| timeband0     | 0.049     | 0.012 | 0.205  |
| timeband0.085 | 0.027     | 0.004 | 0.200  |
| timeband0.162 | 0.024     | 0.003 | 0.177  |
| timeband0.252 | 0.029     | 0.004 | 0.211  |
| timeband0.329 | 0.027     | 0.004 | 0.195  |
| timeband0.413 | 1.486     | 0.521 | 4.239  |
| timeband0.419 | 0.030     | 0.004 | 0.220  |
| timeband0.496 | 2.317     | 0.552 | 9.724  |
| timeband0.498 | 0.390     | 0.053 | 2.865  |
| timeband0.504 | 0.031     | 0.004 | 0.228  |
| timeband0.58  | 0.787     | 0.107 | 5.785  |
| timeband0.583 | 0.792     | 0.108 | 5.821  |
| timeband0.586 | 0.797     | 0.108 | 5.856  |
| timeband0.589 | 0.063     | 0.015 | 0.265  |
| timeband0.665 | 0.402     | 0.055 | 2.957  |
| timeband0.671 | 0.032     | 0.004 | 0.235  |
| timeband0.747 | 0.824     | 0.112 | 6.052  |
| timeband0.75  | 0.413     | 0.056 | 3.033  |
| timeband0.756 | 0.067     | 0.016 | 0.283  |
| timeband0.83  | 1.281     | 0.174 | 9.408  |
| timeband0.832 | 0.063     | 0.015 | 0.264  |
| timeband0.914 | 1.772     | 0.423 | 7.425  |
| timeband0.917 | 0.066     | 0.016 | 0.276  |
| timeband0.999 | 0.100     | 0.031 | 0.329  |
| timeband1.081 | 6.554     | 2.874 | 14.946 |
| timeband1.084 | 0.108     | 0.033 | 0.355  |
| timeband1.166 | 0.998     | 0.136 | 7.311  |
| timeband1.169 | 0.074     | 0.018 | 0.308  |
| timeband1.251 | 0.038     | 0.005 | 0.275  |
| timeband1.333 | 1.051     | 0.144 | 7.687  |
| timeband1.336 | 0.082     | 0.020 | 0.343  |
| timeband1.413 | 1.300     | 0.312 | 5.421  |
| timeband1.418 | 1.113     | 0.152 | 8.146  |
| timeband1.421 | 0.021     | 0.003 | 0.154  |
| timeband1.58  | 0.016     | 0.004 | 0.069  |
| timeband1.999 | 0.052     | 0.007 | 0.382  |
| timeband2.067 | 0.036     | 0.005 | 0.266  |
| timeband2.166 | 1.811     | 0.248 | 13.237 |
| timeband2.168 | 1.216     | 0.166 | 8.891  |
| timeband2.171 | 0.023     | 0.003 | 0.168  |
| timeband2.33  | 0.043     | 0.006 | 0.317  |
| timeband2.415 | 0.088     | 0.021 | 0.367  |
| timeband2.5   | 0.024     | 0.003 | 0.178  |
| timeband2.661 | 0.044     | 0.006 | 0.318  |
| timeband2.752 | 0.016     | 0.002 | 0.120  |
| timeband2.998 | 0.013     | 0.002 | 0.092  |
| timeband3.329 | 0.705     | 0.097 | 5.148  |
| timeband3.335 | 0.026     | 0.004 | 0.189  |
| timeband3.502 | 0.055     | 0.008 | 0.402  |
| timeband3.581 | 0.729     | 0.100 | 5.323  |
| timeband3.587 | 0.018     | 0.003 | 0.134  |
| timeband3.833 | 0.014     | 0.002 | 0.101  |
| timeband4.17  | 0.030     | 0.004 | 0.215  |
| timeband4.331 | 0.009     | 0.001 | 0.063  |

|                  |       |       |        |
|------------------|-------|-------|--------|
| timeband4.914    | 0.034 | 0.005 | 0.245  |
| timeband5.079    | 0.014 | 0.002 | 0.105  |
| timeband5.503    | 0.007 | 0.001 | 0.049  |
| timeband6.587    | 0.049 | 0.007 | 0.354  |
| timeband6.749    | 0.050 | 0.007 | 0.364  |
| timeband6.913    | 2.867 | 0.394 | 20.860 |
| timeband6.916    | 0.022 | 0.003 | 0.158  |
| timeband7.329    | 0.023 | 0.003 | 0.168  |
| timeband7.748    | 0.044 | 0.006 | 0.321  |
| timeband7.984    | 0.010 | 0.001 | 0.074  |
| timeband9.084    | 0.015 | 0.002 | 0.111  |
| timeband9.919    | 0.030 | 0.004 | 0.220  |
| timeband10.42    | 0.013 | 0.002 | 0.097  |
| timeband11.671   | 0.237 | 0.033 | 1.734  |
| timeband11.748   | 0.014 | 0.002 | 0.105  |
| timeband13.166   | 0.134 | 0.018 | 0.979  |
| timeband13.333   | 0.061 | 0.008 | 0.445  |
| timeband13.755   | 0.000 | 0.000 | Inf    |
| sexMale          | 1.015 | 0.663 | 1.554  |
| I((age - 65)/10) | 1.423 | 1.201 | 1.685  |
| st3III           | 1.509 | 0.898 | 2.535  |
| st3IV            | 3.178 | 1.983 | 5.093  |

```
> par(mfrow=c(1,1))
> plot(tbmid, 1000*exp(coef(m2pois1)[1:(ntb-1)]),
+ ylim=c(5,3000), log = "xy", type = "l")
```



Compare the regression coefficients and their error margins to those model `m2haz1`. Do you find any differences? How does the estimated baseline hazard look like?

3. The estimated baseline looks quite ragged when based on 71 separate parameters. A smoothed estimate may be obtained by spline modelling using the tools contained in package `splines` (see the practical of Saturday 25 May afternoon). With the following code you will be able to fit a reasonable spline model for the baseline hazard and draw the estimated curve (together with a band of the 95% confidence limits about the fitted values). From the same model you should also obtain quite familiar results for the rate ratios of interest.

```
> library(splines)
> m2pspli <- update(m2pois1, . ~ ns(stime, df = 6, intercept = F) +
+ sex + I((age-65)/10) + st3)
> round(ci.exp(m2pspli), 3)
```

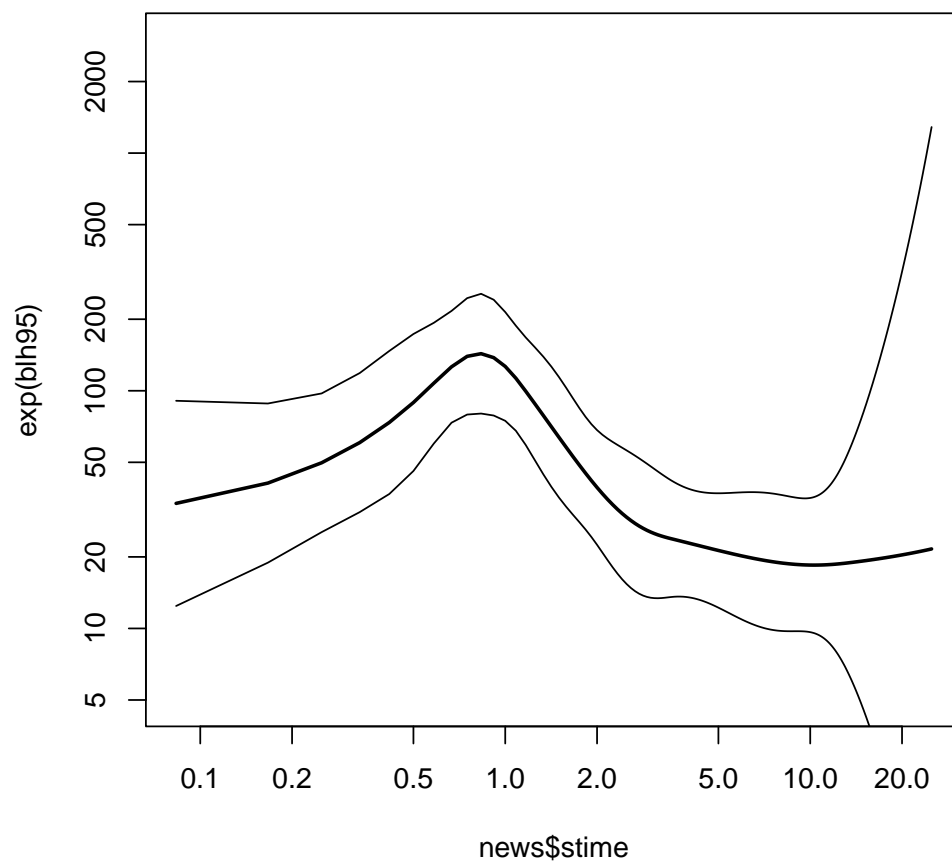
|                                   | exp(Est.) | 2.5%  | 97.5%  |
|-----------------------------------|-----------|-------|--------|
| (Intercept)                       | 0.028     | 0.008 | 0.101  |
| ns(stime, df = 6, intercept = F)1 | 6.505     | 1.776 | 23.823 |
| ns(stime, df = 6, intercept = F)2 | 2.678     | 0.560 | 12.803 |
| ns(stime, df = 6, intercept = F)3 | 0.976     | 0.227 | 4.187  |
| ns(stime, df = 6, intercept = F)4 | 0.423     | 0.105 | 1.699  |
| ns(stime, df = 6, intercept = F)5 | 1.567     | 0.082 | 29.939 |

```

ns(stime, df = 6, intercept = F)6 0.434 0.121 1.558
sexMale 1.021 0.667 1.563
I((age - 65)/10) 1.431 1.208 1.696
st3III 1.514 0.901 2.543
st3IV 3.185 1.988 5.104

> news <- data.frame(stime = seq(0,25, length=301), lex.dur = 1000, sex = "Female",
+ age = 65, st3 = "I-II")
> blhaz <- predict(m2pspli, newdata = news, se.fit = T, type = "link")
> blh95 <- cbind(blhaz$fit, blhaz$se.fit) %*% ci.mat()
> par(mfrow=c(1,1))
> matplot(news$stime, exp(blh95), type = "l", lty = c(1,1,1), lwd = c(2,1,1) ,
+ col = rep("black", 3), log = "xy", ylim = c(5,3000))

```



## 2.13 Time-splitting, time-scales and SMR

This exercise is about mortality among Danish Diabetes patients. It is based on the dataset `DMlate`, a random sample of 10,000 patients from the Danish Diabetes Register (scrambled dates), all with date of diagnosis after 1994.

1. First we load the `Epi` package (and some other packages we will need later):

```
options(width = 90)
library(Epi)
library(popEpi)
library(tidyverse)
library(mgcv)
```

Then we load the dataset and inspect it:

```
data(DMlate)
str(DMlate)

'data.frame': 10000 obs. of 7 variables:
 $ sex : Factor w/ 2 levels "M","F": 2 1 2 2 1 2 1 1 2 1 ...
 $ dobth: num 1940 1939 1918 1965 1933 ...
 $ dodm : num 1999 2003 2005 2009 2009 ...
 $ dodth: num NA NA NA NA NA ...
 $ dooad: num NA 2007 NA NA NA ...
 $ doins: num NA NA NA NA NA NA NA NA NA ...
 $ dox : num 2010 2010 2010 2010 2010 ...
```

```
head(DMlate)

 sex dobth dodm dodth dooad doins dox
50185 F 1940.256 1998.917 NA NA NA 2009.997
307563 M 1939.218 2003.309 NA 2007.446 NA 2009.997
294104 F 1918.301 2004.552 NA NA NA 2009.997
336439 F 1965.225 2009.261 NA NA NA 2009.997
245651 M 1932.877 2008.653 NA NA NA 2009.997
216824 F 1927.870 2007.886 2009.923 NA NA 2009.923
```

```
summary(DMlate)

sex dobth dodm dodth dooad doins
M:5185 Min. :1898 Min. :1995 Min. :1995 Min. :1995 Min. :1995
F:4815 1st Qu.:1930 1st Qu.:2000 1st Qu.:2002 1st Qu.:2001 1st Qu.:2001
 Median :1941 Median :2004 Median :2005 Median :2004 Median :2005
 Mean :1942 Mean :2003 Mean :2005 Mean :2004 Mean :2004
 3rd Qu.:1951 3rd Qu.:2007 3rd Qu.:2008 3rd Qu.:2007 3rd Qu.:2007
 Max. :2008 Max. :2010 Max. :2010 Max. :2010 Max. :2010
 NA's : NA's :7497 NA's :4503 NA's :8209

dox
Min. :1995
1st Qu.:2010
Median :2010
Mean :2009
3rd Qu.:2010
Max. :2010
```

2. We then set up the dataset as a **Lexis** object with age, calendar time and duration of diabetes as timescales, and date of death as event.

In the dataset we have a date of exit, **dox**, which is either the day of censoring or the date of death:

```
with(DMlate, table(dead = !is.na(dodth),
 same = (dodth == dox), exclude = NULL))

 same
dead TRUE <NA>
 FALSE 0 7497
 TRUE 2503 0
```

So we can set up the **Lexis** object by specifying the timescales and the exit status via **!is.na(dodth)**:

```
LL <- Lexis(entry = list(A = dodm-dobth,
 P = dodm,
 dur = 0),
 exit = list(P = dox),
 exit.status = factor(!is.na(dodth),
 labels = c("Alive", "Dead")),
 data = DMlate)
```

NOTE: **entry.status** has been set to "Alive" for all.

NOTE: Dropping 4 rows with duration of follow up < tol

Note that we made sure the the *first* level of **exit.status** is "Alive", because the default is to use the first level as entry status when **entry.status** is not given as argument to **Lexis**.

The 4 persons are persons that have identical date of diabetes and date of death; they can be found by using **keep.dropped = TRUE**:

```
LL <- Lexis(entry = list(A = dodm-dobth,
 P = dodm,
 dur = 0),
 exit = list(P = dox),
 exit.status = factor(!is.na(dodth),
 labels = c("Alive", "Dead")),
 data = DMlate,
 keep.dropped = TRUE)
```

NOTE: **entry.status** has been set to "Alive" for all.

NOTE: Dropping 4 rows with duration of follow up < tol

The dropped rows are in the attribute 'dropped'

To see them type **attr(Obj, 'dropped')**,

to get rid of them type: **attr(Obj, 'dropped') <- NULL**

- where 'Obj' is the name of your **Lexis** object

The dropped persons are:

```
attr(LL, 'dropped')
```

```

 sex dobth dodm dodth dooad doins dox
173047 M 1917.863 1999.457 1999.457 NA NA 1999.457
361856 F 1936.067 1996.984 1996.984 NA NA 1996.984
245324 M 1917.877 1999.906 1999.906 NA NA 1999.906
318694 F 1919.060 2006.794 2006.794 NA NA 2006.794

```

We can get an overview of the data by using the `summary` function on the object:

```

summary(LL)
Transitions:
 To
From Alive Dead Records: Events: Risk time: Persons:
 Alive 7497 2499 9996 2499 54273.27 9996

head(LL)

```

```

lex.id A P dur lex.dur lex.Cst lex.Xst sex dobth dodm dodth dooad
1 58.66 1998.92 0 11.08 Alive Alive F 1940.256 1998.917 NA NA
2 64.09 2003.31 0 6.69 Alive Alive M 1939.218 2003.309 NA 2007.446
3 86.25 2004.55 0 5.45 Alive Alive F 1918.301 2004.552 NA NA
4 44.04 2009.26 0 0.74 Alive Alive F 1965.225 2009.261 NA NA
5 75.78 2008.65 0 1.34 Alive Alive M 1932.877 2008.653 NA NA
6 80.02 2007.89 0 2.04 Alive Dead F 1927.870 2007.886 2009.923 NA
doins dox
NA 2009.997
NA 2009.997
NA 2009.997
NA 2009.997
NA 2009.997
NA 2009.997
NA 2009.923

```

3. A crude picture of the mortality by sex can be obtained by the `stat.table` function:

```

stat.table(sex,
 list(D = sum(lex.Xst == "Dead"),
 Y = sum(lex.dur),
 rate = ratio(lex.Xst == "Dead", lex.dur, 1000)),
 margins = TRUE,
 data = LL)

```

```

sex D Y rate

M 1343.00 27614.21 48.63
F 1156.00 26659.05 43.36

Total 2499.00 54273.27 46.04

```

So not surprising, we see that men have a higher mortality than women, here apparently only some 10%.

4. When we want to assess how mortality depends on age, calendar time and duration or to compare with population mortality, we would in principle split the follow-up along all three time scales, but in practice it is sufficient to split it along one of the time-scales

and then use the value of each of the time-scales at the left endpoint of the intervals for analysis and for matching with population mortality. Note however that this requires that time-scales are treated as *quantitative* variables in the modeling.

We note that the total follow-up time was some 54,000 person-years, so if we split the follow-up in 6-month intervals we should get a bit more than 110,000 records. Note that in the `popEpi` package there is a function with the same functionality, which is faster (particularly for large datasets) and has a somewhat smarter syntax — it returns a `data.table`:

```
system.time(SL <- splitLexis(LL, breaks = seq(0,125,1/2), time.scale = "A"))

 user system elapsed
2.733 0.108 2.842

summary(SL) ; class(SL)

Transitions:
 To
From Alive Dead Records: Events: Risk time: Persons:
 Alive 115974 2499 118473 2499 54273.27 9996

[1] "Lexis" "data.frame"

system.time(SL <- splitMulti(LL, A = seq(0,125,1/2)))

 user system elapsed
1.454 0.068 1.522

summary(SL) ; class(SL)

Transitions:
 To
From Alive Dead Records: Events: Risk time: Persons:
 Alive 115974 2499 118473 2499 54273.27 9996

[1] "Lexis" "data.table" "data.frame"

summary(LL)

Transitions:
 To
From Alive Dead Records: Events: Risk time: Persons:
 Alive 7497 2499 9996 2499 54273.27 9996
```

We see that the number of records have increased, but the number of persons, events and person-years is still the same as in LL. Thus, the amount of follow-up information is still the same; it is just distributed over more records, and hence allowing more detailed analyses.



## Age-specific mortality

5. We now use this dataset to estimate models with age-specific mortality curves for men and women separately, using splines (the function `gam`, using `s` from the `mgcv` package).

```
r.m <- gam(cbind(lex.Xst == "Dead", lex.dur) ~ s(A, k = 20),
 family = poisreg,
 data = subset(SL, sex == "M"))
r.f <- update(r.m, data = subset(SL, sex == "F"))
```

Here we are modeling the rates based on the follow-up (events (`lex.Xst == "Dead"`)) and person-years (`lex.dur`)) as a non-linear function of age — represented by the penalized spline function `s`.

There is a convenient wrapper for this, exploiting the `Lexis` structure of data, which however does not have an `update` method to it.

```
r.m <- gam.Lexis(subset(SL, sex == "M"), ~ s(A, k = 20))
mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "M") with log link:
Rates for the transition:
Alive->Dead

r.f <- gam.Lexis(subset(SL, sex == "F"), ~ s(A, k = 20))
mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "F") with log link:
Rates for the transition:
Alive->Dead
```

6. From these objects we could get the estimated log-rates by using `predict`, by supplying a data frame of values for the variables used as predictors in the model. These will be values of age — the ages where we want to see the predicted rates *and* `lex.dur`.

The default `predict.gam` function is a bit clunky as it gives the prediction and the standard errors of these in two different elements of a list, so in `Epi` there is a wrapper function `ci.pred` that uses this and computes predicted rates and confidence limits for these, which is usually what is needed.

Note that in terms of predictions from a model fitted with the family `poisson`, `lex.dur` is a covariate too; by setting this to 1000 throughout the data frame and we get the rates in units of deaths per 1000 PY<sup>1</sup>

However, when using the `glm.Lexis` or `gam.Lexis` we avoid this; they rely on the `poisreg` family that will return the rates in the (inverse) units in which the person-years were given; that is the units of `lex.dur`, in this case, events per 1 person-year:

```
nd <- data.frame(A = seq(20, 80, 0.5))
p.m <- ci.pred(r.m, newdata = nd)
p.f <- ci.pred(r.f, newdata = nd)
head(p.m)
```

---

<sup>1</sup>Note however this is only the case if the offset is specified in the model formula. If the offset is specified as an argument (`offset = log(lex.dur)`), then the value of `lex.dur` in the dataframe will be ignored (equivalent of setting `lex.dur` to 1 in the `newdata` argument to `ci.pred`.)

|   | Estimate    | 2.5%         | 97.5%       |
|---|-------------|--------------|-------------|
| 1 | 0.001321917 | 0.0003848770 | 0.004540318 |
| 2 | 0.001367826 | 0.0004108868 | 0.004553436 |
| 3 | 0.001415522 | 0.0004384736 | 0.004569722 |
| 4 | 0.001465092 | 0.0004677224 | 0.004589250 |
| 5 | 0.001516628 | 0.0004987243 | 0.004612088 |
| 6 | 0.001570226 | 0.0005315767 | 0.004638295 |

7. We can then plot the predicted rates for men and women together using `matplot`:

```
matplot(nd$A, cbind(p.m, p.f) * 1000,
 type = "l", col = rep(c("blue", "red"), each = 3), lwd = c(3, 1, 1), lty = 1,
 log = "y", xlab = "Age", ylab = "Mortality of DM ptt per 1000 PY")
```

An alternative is to use `matshade` that gives confidence limits as shaded areas

```
matshade(nd$A, cbind(p.m, p.f) * 1000, plot = TRUE,
 col = c("blue", "red"), lty = 1, lwd = 3,
 log = "y", xlab = "Age", ylab = "Mortality among DM ptt per 1000 PY")
```

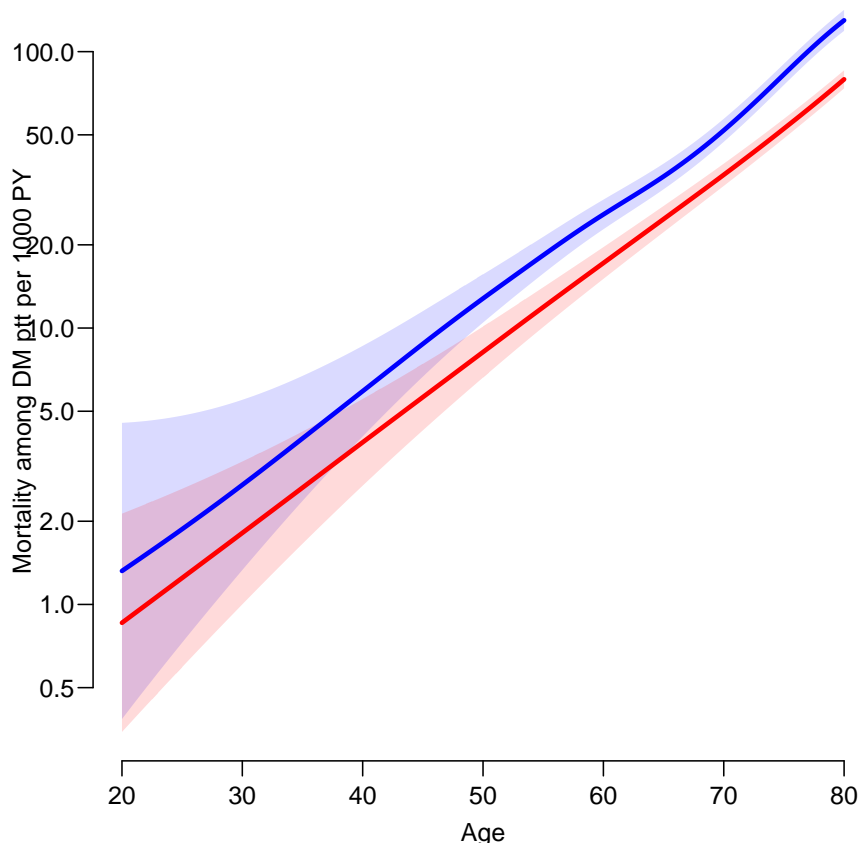


Figure 2.1: Age-specific mortality rates for Danish diabetes patients as estimated from a `gam` model with only age. Blue: men, red: women.

Not surprisingly, the uncertainty on the rates is largest among the youngest where the no. of deaths is smallest.

## Further time scales: period and duration

8. We model the mortality rates among diabetes patients also including current date and duration of diabetes. Note that we for later prediction purposes put the offset in the model formula.

```
Mcr <- gam.Lexis(subset(SL, sex == "M"),
 ~ s(A, bs = "cr", k = 10) +
 s(P, bs = "cr", k = 10) +
 s(dur, bs = "cr", k = 10))

mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "M") with log link:
Rates for the transition:
Alive->Dead

summary(Mcr)

Family: poisson
Link function: log

Formula:
cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 10)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.54074 0.04938 -71.7 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 3.645 4.517 1013.20 < 2e-16 ***
s(P) 1.024 1.048 17.58 3.48e-05 ***
s(dur) 7.586 8.384 74.46 < 2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.00333 Deviance explained = 9.87%
UBRE = -0.8054 Scale est. = 1 n = 60347

Fcr <- gam.Lexis(subset(SL, sex == "F"),
 ~ s(A, bs = "cr", k = 10) +
 s(P, bs = "cr", k = 10) +
 s(dur, bs = "cr", k = 10))

mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "F") with log link:
Rates for the transition:
Alive->Dead

summary(Fcr)

Family: poisson
Link function: log

Formula:
cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 10)
```

```

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.78483 0.05808 -65.17 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 2.667 3.366 988.49 < 2e-16 ***
s(P) 1.904 2.391 20.08 0.000136 ***
s(dur) 5.973 6.972 38.98 < 2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.00417 Deviance explained = 11.1%
UBRE = -0.82405 Scale est. = 1 n = 58126

```

For the male rates the `edf` (effective degrees of freedom) is quite close to the `k`, but as we shall see there is no need for more detailed modeling.

9. We can now plot the estimated effects for men and women — compare the different plotting options between men and women:

```

par(mfcol = c(3,2))
plot(Fcr, ylim = c(-3,3), col = "red")
plot(Mcr, ylim = c(-3,3), col = "blue",
 lwd = 2, shade = TRUE, shade.col = adjustcolor("blue", alpha = 0.15))

```

10. Not surprisingly, these models fit substantially better than the model with only age as we can see from this comparison:

```

anova(Mcr, r.m, test = "Chisq")

```

Analysis of Deviance Table

```

Model 1: cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 10)
Model 2: cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 k = 20)

```

|   | Resid. | Df | Resid. Dev | Df      | Deviance | Pr(>Chi)      |
|---|--------|----|------------|---------|----------|---------------|
| 1 | 60332  |    | 11717      |         |          |               |
| 2 | 60340  |    | 11812      | -7.9484 | -95.094  | < 2.2e-16 *** |

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

anova(Fcr, r.f, test = "Chisq")

```

Analysis of Deviance Table

```

Model 1: cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 10)
Model 2: cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 k = 20)

```

|   | Resid. | Df | Resid. Dev | Df      | Deviance | Pr(>Chi)      |
|---|--------|----|------------|---------|----------|---------------|
| 1 | 60332  |    | 11717      |         |          |               |
| 2 | 60340  |    | 11812      | -7.9484 | -95.094  | < 2.2e-16 *** |

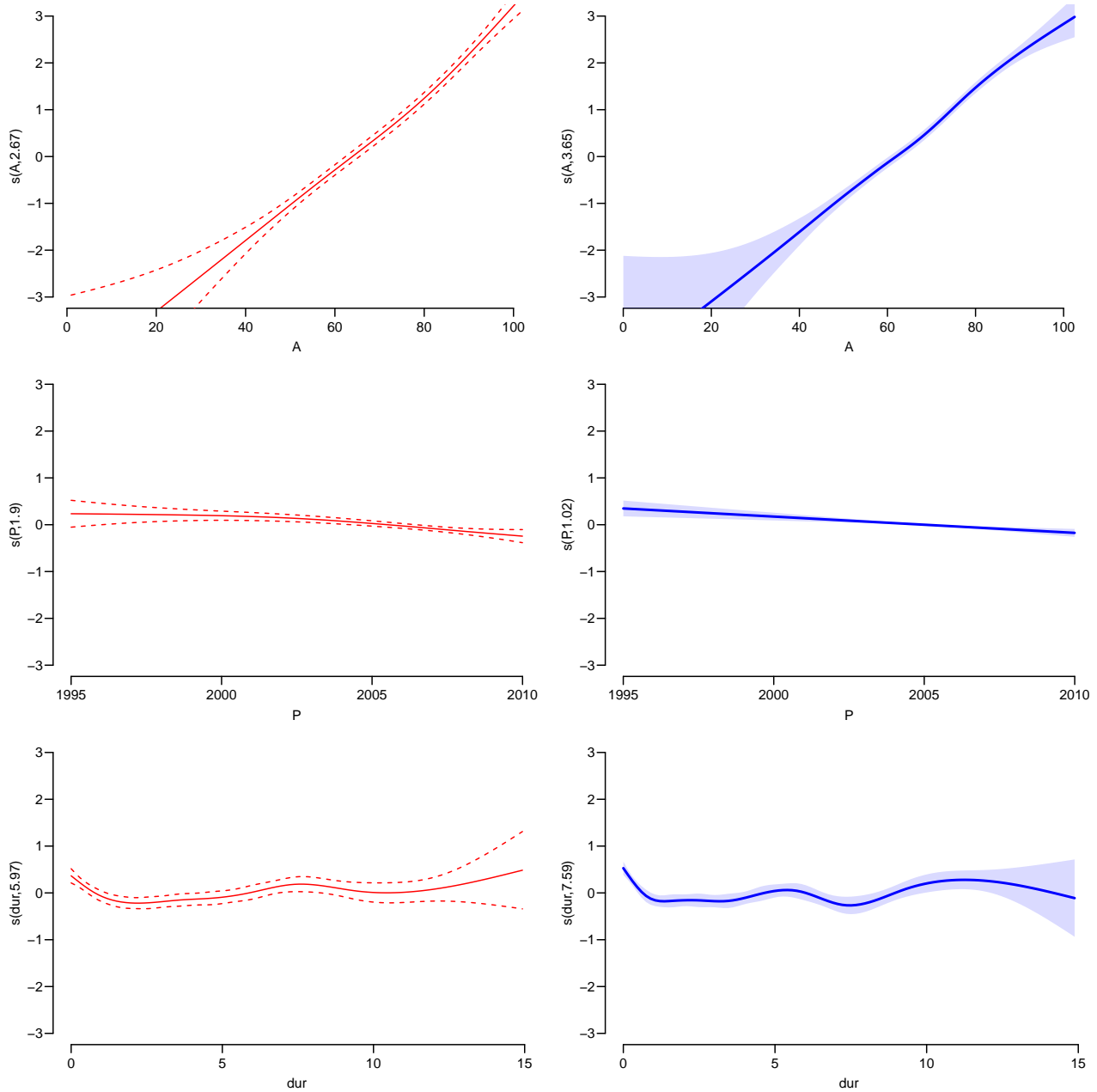


Figure 2.2: Plot of the estimated smooth terms for women (left) and men (right). It seems that the duration effects are somewhat over-modeled.

```

1 58112 10204
2 58122 10268 -9.3976 -63.385 4.491e-10 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

11. Since the fitted model has three time-scales: current age, current date and current duration of diabetes, the effects that we see from the `plot.gam` are not really interpretable; they are (as in any kind of multiple regressions) to be interpreted as “all else equal” which they are not; the three time scales advance simultaneously at the same pace.

The reporting would therefore more naturally be *only* on one time scale, showing the mortality for persons diagnosed in different ages in a given year.

This is most easily done using the `ci.pred` function with the `newdata=` argument. So a person diagnosed in age 50 in 1995 will have a mortality measured in cases per 1000 PY as:

```
pts <- seq(0, 12, 1/4)
nd <- data.frame(A = 50 + pts,
 P = 1995 + pts,
 dur = pts)
head(cbind(nd$A, ci.pred(Mcr, newdata = nd) * 1000))
```

|         | Estimate | 2.5%     | 97.5%    |
|---------|----------|----------|----------|
| 1 50.00 | 29.75850 | 22.91422 | 38.64712 |
| 2 50.25 | 23.84929 | 18.78300 | 30.28211 |
| 3 50.50 | 19.60327 | 15.38916 | 24.97137 |
| 4 50.75 | 16.95027 | 13.21805 | 21.73631 |
| 5 51.00 | 15.71774 | 12.31854 | 20.05491 |
| 6 51.25 | 15.41895 | 12.12649 | 19.60534 |

Note that because we used `gam.Lexis` which uses the `thepoisreg` family, we need not specify `lex.dur` as a variable in the prediction data frame `nd`. Predictions will be rates in the same (well, inverse) units as `lex.dur`.

Since there is no duration beyond 18 years in the dataset we only make predictions for 12 years of duration, and do it for persons diagnosed in 1995 and 2005 — the latter is quite dubious too because we are extrapolating calendar time trends quite a bit beyond data.

We form matrices of predictions with confidence intervals, that we will plot in the same frame (sing nested loops):

```
plot(NA, xlim = c(50, 85), ylim = c(5, 400), log = "y",
 xlab = "Age", ylab = "Mortality rate for DM patients")
for(ip in c(1995, 2005))
 for(ia in c(50, 60, 70))
 {
 nd <- data.frame(A = ia + pts,
 P = ip + pts,
 dur = pts)
 matshade(nd$A, ci.pred(Mcr, nd) * 1000, col = "blue", lty = 1 + (ip == 1995))
 matshade(nd$A, ci.pred(Fcr, nd) * 1000, col = "red", lty = 1 + (ip == 1995))
 }
```

- From figure 2.3 it seems that the duration effect is dramatically over-modeled, so we refit constraining the d.f. to 5 (note that this choice is essentially an arbitray choice) and redo the whole thing again:

```
Mcr <- gam.Lexis(subset(SL, sex == "M"),
 ~ s(A, bs = "cr", k = 10) +
 s(P, bs = "cr", k = 10) +
 s(dur, bs = "cr", k = 5))
```

mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "M") with log link:  
 Rates for the transition:  
 Alive->Dead

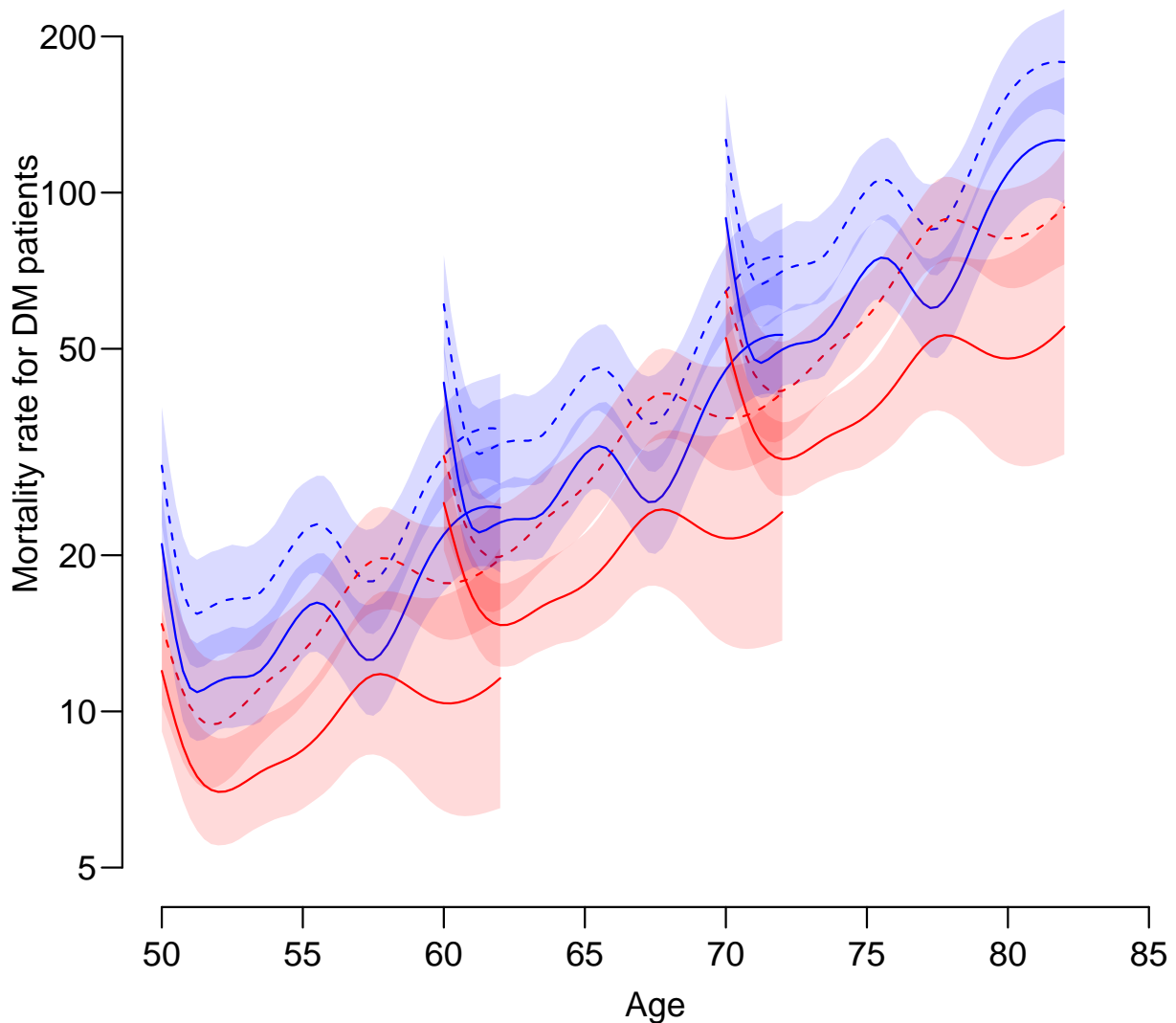


Figure 2.3: Mortality rates for diabetes patients diagnosed 1995 and 2005 in ages 50, 60 and 70; as estimated by penalized splines. Men blue, women red; broken lines persons diagnosed 1995, full lines persons diagnosed 2005.

```
summary(Mcr)

Family: poisson
Link function: log

Formula:
cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 5)

Parametric coefficients:
```

```

 Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.54055 0.04943 -71.63 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 3.697 4.575 1014.15 < 2e-16 ***
s(P) 1.025 1.049 17.54 3.58e-05 ***
s(dur) 3.935 3.997 55.70 < 2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.0033 Deviance explained = 9.72%
UBRE = -0.80521 Scale est. = 1 n = 60347

Fcr <- gam.Lexis(subset(SL, sex == "F"),
 ~ s(A, bs = "cr", k = 10) +
 s(P, bs = "cr", k = 10) +
 s(dur, bs = "cr", k = 5))

mgcv::gam Poisson analysis of Lexis object subset(SL, sex == "F") with log link:
Rates for the transition:
Alive->Dead

summary(Fcr)

Family: poisson
Link function: log

Formula:
cbind(trt(Lx$lex.Cst, Lx$lex.Xst) %in% trnam, Lx$lex.dur) ~ s(A,
 bs = "cr", k = 10) + s(P, bs = "cr", k = 10) + s(dur, bs = "cr",
 k = 5)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.78590 0.05799 -65.28 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 2.645 3.339 987.07 < 2e-16 ***
s(P) 1.917 2.408 20.16 0.000136 ***
s(dur) 3.797 3.972 34.98 2.78e-06 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = 0.00416 Deviance explained = 11%
UBRE = -0.824 Scale est. = 1 n = 58126

gam.check(Mcr)

Method: UBRE Optimizer: outer newton
full convergence after 4 iterations.
Gradient range [-7.80242e-07,2.43377e-10]
(score -0.8052124 & scale 1).
Hessian positive definite, eigenvalue range [7.531598e-07,1.060907e-05].
Model rank = 23 / 23

```



Basis dimension (k) checking results. Low p-value (k-index<1) may indicate that k is too low, especially if edf is close to k'.

```

 k' edf k-index p-value
s(A) 9.00 3.70 0.91 0.055 .
s(P) 9.00 1.02 0.93 0.285
s(dur) 4.00 3.94 0.94 0.525

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```
gam.check(Fcr)
```

```

Method: UBRE Optimizer: outer newton
full convergence after 6 iterations.
Gradient range [8.430318e-09,5.299758e-07]
(score -0.8240013 & scale 1).
Hessian positive definite, eigenvalue range [5.823044e-06,1.937887e-05].
Model rank = 23 / 23

```

Basis dimension (k) checking results. Low p-value (k-index<1) may indicate that k is too low, especially if edf is close to k'.

```

 k' edf k-index p-value
s(A) 9.00 2.64 0.88 0.065 .
s(P) 9.00 1.92 0.92 0.765
s(dur) 4.00 3.80 0.89 0.105

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

From the summaries it seems that  $k = 5$  is a bit *under*-modeling the duration effect.

We can also add the rate-ratio between men and women using the `ci.ratio` function:

```

plot(NA, xlim = c(50,80), ylim = c(0.9,100), log = "y",
 xlab = "Age", ylab = "Mortality rate for DM patients")
abline(v = c(50,55,60,65,70), col = gray(0.8))
for(ip in c(1995,2005))
ip <- 2005
for(ia in seq(50, 70, 5))
{
 nd <- data.frame(A = ia + pts,
 P = ip + pts,
 dur = pts)
 matshade(nd$A, rm <- ci.pred(Mcr, nd) * 1000, col = "blue", lwd = 2)
 matshade(nd$A, rf <- ci.pred(Fcr, nd) * 1000, col = "red", lwd = 2)
 matshade(nd$A, ci.ratio(rm, rf), lwd = 2)
}
abline(h = 1, lty = "55")

```

From figure ?? we see that there is an increased mortality in the first few years after diagnosis (this is a clinical artifact) and little indication that age *at* diagnosis has any effect. (This can of course be tried explicitly).

Moreover it is pretty clear that the M/W mortality rate ratio is constant across age and duration.

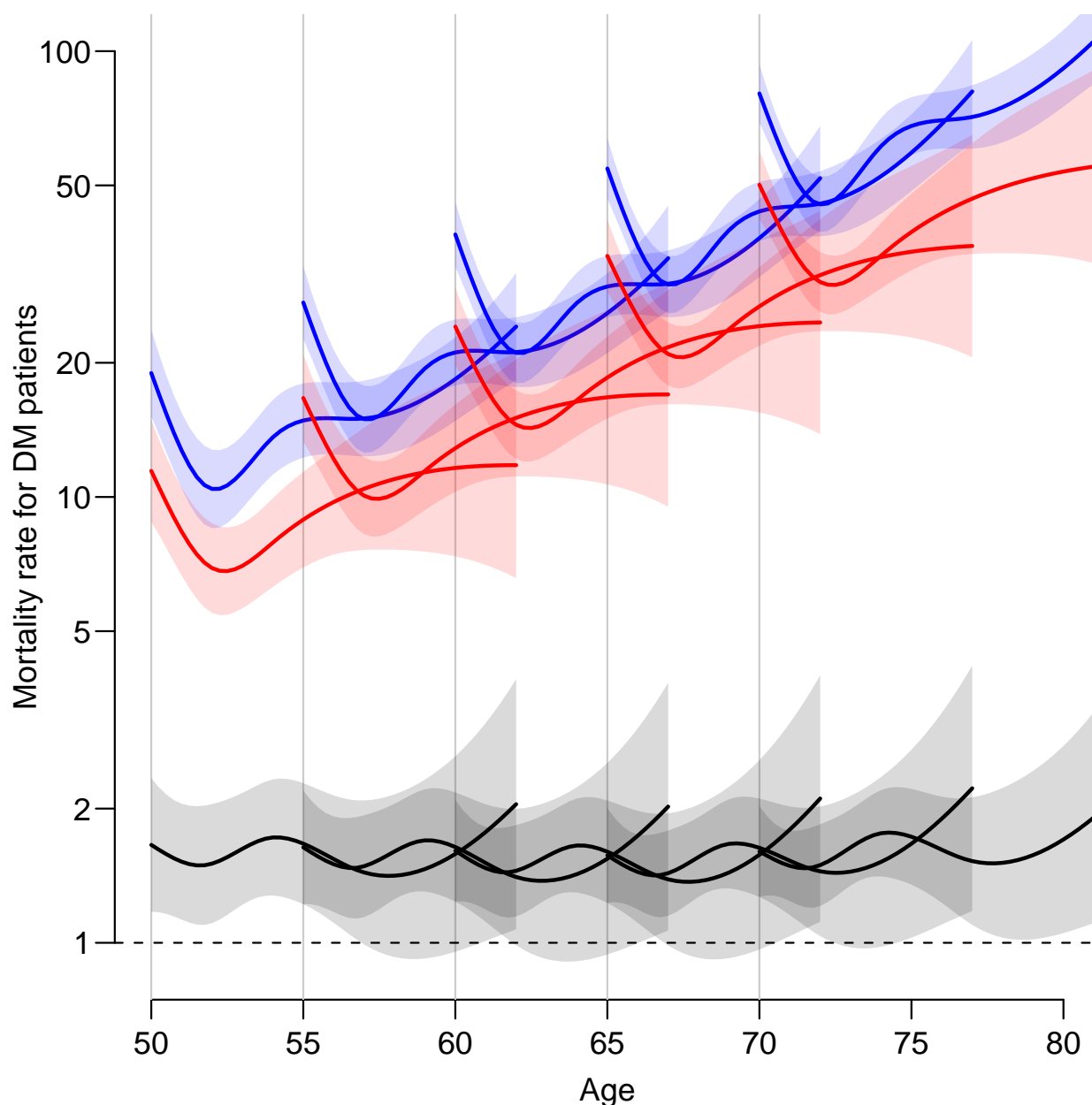


Figure 2.4: *Mortality rates for diabetes patients diagnosed 1995 and 2005 in ages 50, 55, 60, 65 and 70; as estimated by penalized splines. Note that we did this for year of diagnosis 2005 alone, but for a longer duration period. Men blue, women red, M/W rate ratio gray.*

## SMR

The SMR is the **Standardized Mortality Ratio**, which is the mortality rate-ratio between the diabetes patients and the general population. In real studies we would subtract the deaths and the person-years among the diabetes patients from those of the general population, but since we do not have access to these, we make the comparison to the general population at large, *i.e.* also including the diabetes patients.

We now want to include the population mortality rates as a fixed variable in the split dataset; for each record in the split dataset we attach the value of the population mortality

for the relevant sex, and and calendar time.

This can be achieved in two ways: Either we just use the current split of follow-up time and allocate the population mortality rates for some suitably chosen (mid-)point of the follow-up in each, or we make a second split by date, so that follow-up in the diabetes patients is in the same classification of age and data as the population mortality table.

13. Using the former approach we shall include as an extra variable the population mortality as available from the data set `M.dk`.

First create the variables in the diabetes dataset that we need for matching with the age and period classification of the population mortality data, that is age, date (and sex) at the midpoint of each of the intervals (or rather at a point 3 months after the left endpoint of the interval — recall we split the follow-up in 6 month intervals).

We need to have variables of the same type when we merge, so we must transform the sex variable in `M.dk` to a factor, and must for each follow-up interval in the `SL` data have an age (`Am`) and a period (`Pm`) variable that can be used in merging with the population data. We match on the age and period of the midpoint of the follow-up interval:

```
SL$Am <- floor(SL$A + 0.25)
SL$Pm <- floor(SL$P + 0.25)
```

Then we can load the dataset with the rates and construct the matching variables:

```
data(M.dk)
str(M.dk)

'data.frame': 7800 obs. of 6 variables:
 $ A : num 0 0 0 0 0 0 0 0 0 0 ...
 $ sex : num 1 2 1 2 1 2 1 2 1 2 ...
 $ P : num 1974 1974 1975 1975 1976 ...
 $ D : num 459 303 435 311 405 258 332 205 312 233 ...
 $ Y : num 35963 34383 36099 34652 34965 ...
 $ rate: num 12.76 8.81 12.05 8.97 11.58 ...
 - attr(*, "Contents")= chr "Number of deaths and risk time in Denmark"

M.dk <- transform(M.dk, Am = A,
 Pm = P,
 sex = factor(sex, labels = c("M", "F")))

head(M.dk)

 A sex P D Y rate Am Pm
1 0 M 1974 459 35963.33 12.762999 0 1974
2 0 F 1974 303 34382.83 8.812537 0 1974
3 0 M 1975 435 36099.00 12.050195 0 1975
4 0 F 1975 311 34652.17 8.974908 0 1975
5 0 M 1976 405 34965.00 11.583012 0 1976
6 0 F 1976 258 33278.33 7.752792 0 1976

str(SL)

Classes 'Lexis', 'data.table' and 'data.frame': 118473 obs. of 16 variables:
 $ lex.id : int 1 1 1 1 1 1 1 1 1 1 ...
 $ A : num 58.7 59 59.5 60 60.5 ...
 $ P : num 1999 1999 2000 2000 2001 ...
 $ dur : num 0 0.339 0.839 1.339 1.839 ...
 $ lex.dur: num 0.339 0.5 0.5 0.5 0.5 ...
```

```

$ lex.Cst: Factor w/ 2 levels "Alive","Dead": 1 1 1 1 1 1 1 1 1 1 ...
$ lex.Xst: Factor w/ 2 levels "Alive","Dead": 1 1 1 1 1 1 1 1 1 1 ...
$ sex : Factor w/ 2 levels "M","F": 2 2 2 2 2 2 2 2 2 2 ...
$ dobth : num 1940 1940 1940 1940 1940 ...
$ dodm : num 1999 1999 1999 1999 1999 ...
$ dodth : num NA NA NA NA NA NA NA NA NA NA ...
$ dooad : num NA NA NA NA NA NA NA NA NA NA ...
$ doins : num NA NA NA NA NA NA NA NA NA NA ...
$ dox : num 2010 2010 2010 2010 2010 ...
$ Am : num 58 59 59 60 60 61 61 62 62 63 ...
$ Pm : num 1999 1999 2000 2000 2000 2001 ...
- attr(*, ".internal.selfref")=<externalptr>
- attr(*, "time.scales")= chr [1:3] "A" "P" "dur"
- attr(*, "time.since")= chr [1:3] "" "" ""
- attr(*, "breaks")=List of 3
..$ A : num [1:251] 0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 ...
..$ P : NULL
..$ dur: NULL

```

```
str(M.dk)
```

```

'data.frame': 7800 obs. of 8 variables:
 $ A : num 0 0 0 0 0 0 0 0 0 0 ...
 $ sex : Factor w/ 2 levels "M","F": 1 2 1 2 1 2 1 2 1 2 ...
 $ P : num 1974 1974 1975 1975 1976 ...
 $ D : num 459 303 435 311 405 258 332 205 312 233 ...
 $ Y : num 35963 34383 36099 34652 34965 ...
 $ rate : num 12.76 8.81 12.05 8.97 11.58 ...
 $ Am : num 0 0 0 0 0 0 0 0 0 0 ...
 $ Pm : num 1974 1974 1975 1975 1976 ...

```

We then match the rates from `M.dk` into `SL` — `sex`, `Am` and `Pm` are the common variables, and therefore the match is on these variables:

```

SLr <- merge(SL, M.dk[,c("sex", "Am", "Pm", "rate")])
dim(SLr)

[1] 118473 16

dim(SLr)

[1] 118454 17

```

This merge only takes rows that have information from both data sets, hence the slightly fewer rows in `SLr` than in `SL` — there are a few record in `SL` with age and period values that do not exist in the population mortality data, these will be excluded.

This could also have been done as an `inner_join` using the `tidyverse` machinery:

```

SLi <- inner_join(SL, M.dk[,c("sex", "Am", "Pm", "rate")])
dim(SLi)

[1] 118473 16

dim(SLi)

[1] 118454 17

```

14. We compute the expected number of deaths as the person-time multiplied by the corresponding population rate recalling that the rate is given in units of deaths per 1000 PY, whereas `lex.dur` is in units of 1 PY:

```
SLr$E <- SLr$lex.dur * SLr$rate / 1000
stat.table(sex,
 list(D = sum(lex.Xst == "Dead"),
 Y = sum(lex.dur),
 E = sum(E),
 SMR = ratio(lex.Xst == "Dead", E)),
 data = SLr,
 margin = TRUE)
```

| sex   | D       | Y        | E       | SMR  |
|-------|---------|----------|---------|------|
| M     | 1342.00 | 27611.40 | 796.11  | 1.69 |
| F     | 1153.00 | 26654.52 | 747.77  | 1.54 |
| Total | 2495.00 | 54265.91 | 1543.88 | 1.62 |

```
stat.table(list(sex,
 Age = cut(A,
 breaks = c(0, 4:9*10, 100),
 right = FALSE)),
 list(D = sum(lex.Xst == "Dead"),
 Y = sum(lex.dur),
 E = sum(E),
 SMR = ratio(lex.Xst == "Dead", E)),
 margin = TRUE,
 data = SLr)
```

| sex   | Age     |         |          |          |          |         |          | Total    |
|-------|---------|---------|----------|----------|----------|---------|----------|----------|
|       | [0,40)  | [40,50) | [50,60)  | [60,70)  | [70,80)  | [80,90) | [90,100) |          |
| M     | 6.00    | 32.00   | 119.00   | 275.00   | 486.00   | 348.00  | 76.00    | 1342.00  |
|       | 2129.67 | 3034.15 | 6273.51  | 7940.22  | 5842.90  | 2165.80 | 225.14   | 27611.40 |
|       | 1.94    | 9.47    | 48.48    | 142.38   | 275.67   | 254.92  | 63.26    | 796.11   |
|       | 3.09    | 3.38    | 2.45     | 1.93     | 1.76     | 1.37    | 1.20     | 1.69     |
| F     | 5.00    | 15.00   | 62.00    | 157.00   | 331.00   | 423.00  | 160.00   | 1153.00  |
|       | 2576.33 | 2742.03 | 4491.68  | 6112.30  | 6383.09  | 3786.78 | 562.31   | 26654.52 |
|       | 1.24    | 5.01    | 22.00    | 74.00    | 204.44   | 318.81  | 122.26   | 747.77   |
|       | 4.02    | 2.99    | 2.82     | 2.12     | 1.62     | 1.33    | 1.31     | 1.54     |
| Total | 11.00   | 47.00   | 181.00   | 432.00   | 817.00   | 771.00  | 236.00   | 2495.00  |
|       | 4706.00 | 5776.18 | 10765.19 | 14052.52 | 12225.99 | 5952.59 | 787.46   | 54265.91 |
|       | 3.18    | 14.48   | 70.47    | 216.39   | 480.11   | 573.73  | 185.51   | 1543.88  |
|       | 3.45    | 3.25    | 2.57     | 2.00     | 1.70     | 1.34    | 1.27     | 1.62     |

We see that the SMR is pretty much the same for women and men, but also that there is quite a steep decrease in SMR by age.

15. We can fit a poisson model with sex as the explanatory variable and log-expected as offset to derive the SMR (and c.i.).

Some of the population mortality rates are 0, so we must exclude those records from the analysis.

```
msmr <- glm((lex.Xst == "Dead") ~ sex - 1 + offset(log(E)),
 family = poisson,
 data = subset(SLr, E > 0))
ci.exp(msmr)

 exp(Est.) 2.5% 97.5%
sexM 1.685699 1.597881 1.778344
sexF 1.541922 1.455442 1.633540
```

These are the same SMRs as just coomputed by `stat.table`, but now with confidence intervals.

16. The same model can be fitted a bit simpler by the `poisreg` family:

```
msmr <- glm(cbind(lex.Xst == "Dead", E) ~ sex - 1,
 family = poisreg,
 data = subset(SLr, E > 0))
ci.exp(msmr)

 exp(Est.) 2.5% 97.5%
sexM 1.685699 1.597881 1.778344
sexF 1.541922 1.455441 1.633541
```

We can assess the ratio of SMRs between men and women by using the `ctr.mat` argument which should be a matrix:

```
(CM <- rbind(M = c(1,0),
 W = c(0,1),
 'M/F' = c(1,-1)))

 [,1] [,2]
M 1 0
W 0 1
M/F 1 -1

round(ci.exp(msmr, ctr.mat = CM), 2)

 exp(Est.) 2.5% 97.5%
M 1.69 1.60 1.78
W 1.54 1.46 1.63
M/F 1.09 1.01 1.18
```

### 2.13.1 SMR modeling

17. We can treat SMR exactly as mortality rates by using the expected numbers instead of the person-years.

We exclude those records where no deaths in the population occur (that is where the rate, and hence the expected number is 0) — you could say that this corresponds to parts of the data where no follow-up on the population mortality scale is available. The rest is essentially just a repeat of the analyses for mortality rates:

```

Msmr <- gam(cbind(lex.Xst == "Dead", E) ~ s(A, bs = "cr", k = 10) +
 s(P, bs = "cr", k = 10) +
 s(dur, bs = "cr", k = 5),
 family = poisreg,
 data = subset(SLr, E > 0 & sex == "M"))
Fsmr <- update(Msmr, data = subset(SLr, E > 0 & sex == "F"))
summary(Msmr)
Family: poisson
Link function: log

Formula:
cbind(lex.Xst == "Dead", E) ~ s(A, bs = "cr", k = 10) + s(P,
 bs = "cr", k = 10) + s(dur, bs = "cr", k = 5)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.77310 0.04086 18.92 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 1.017 1.033 58.663 <2e-16 ***
s(P) 1.006 1.011 1.973 0.162
s(dur) 3.914 3.995 55.703 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = -0.000399 Deviance explained = 0.991%
UBRE = -0.80531 Scale est. = 1 n = 60333

summary(Fsmr)
Family: poisson
Link function: log

Formula:
cbind(lex.Xst == "Dead", E) ~ s(A, bs = "cr", k = 10) + s(P,
 bs = "cr", k = 10) + s(dur, bs = "cr", k = 5)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.75476 0.05389 14.01 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(A) 1.672 2.111 56.02 < 2e-16 ***
s(P) 7.925 8.657 16.79 0.0751 .
s(dur) 3.800 3.973 36.55 1.35e-06 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = -0.00054 Deviance explained = 1.04%
UBRE = -0.8241 Scale est. = 1 n = 58099

par(mfcol = c(3,2))
plot(Msmr, ylim = c(-1,2), col = "blue")
plot(Fsmr, ylim = c(-1,2), col = "red")

```

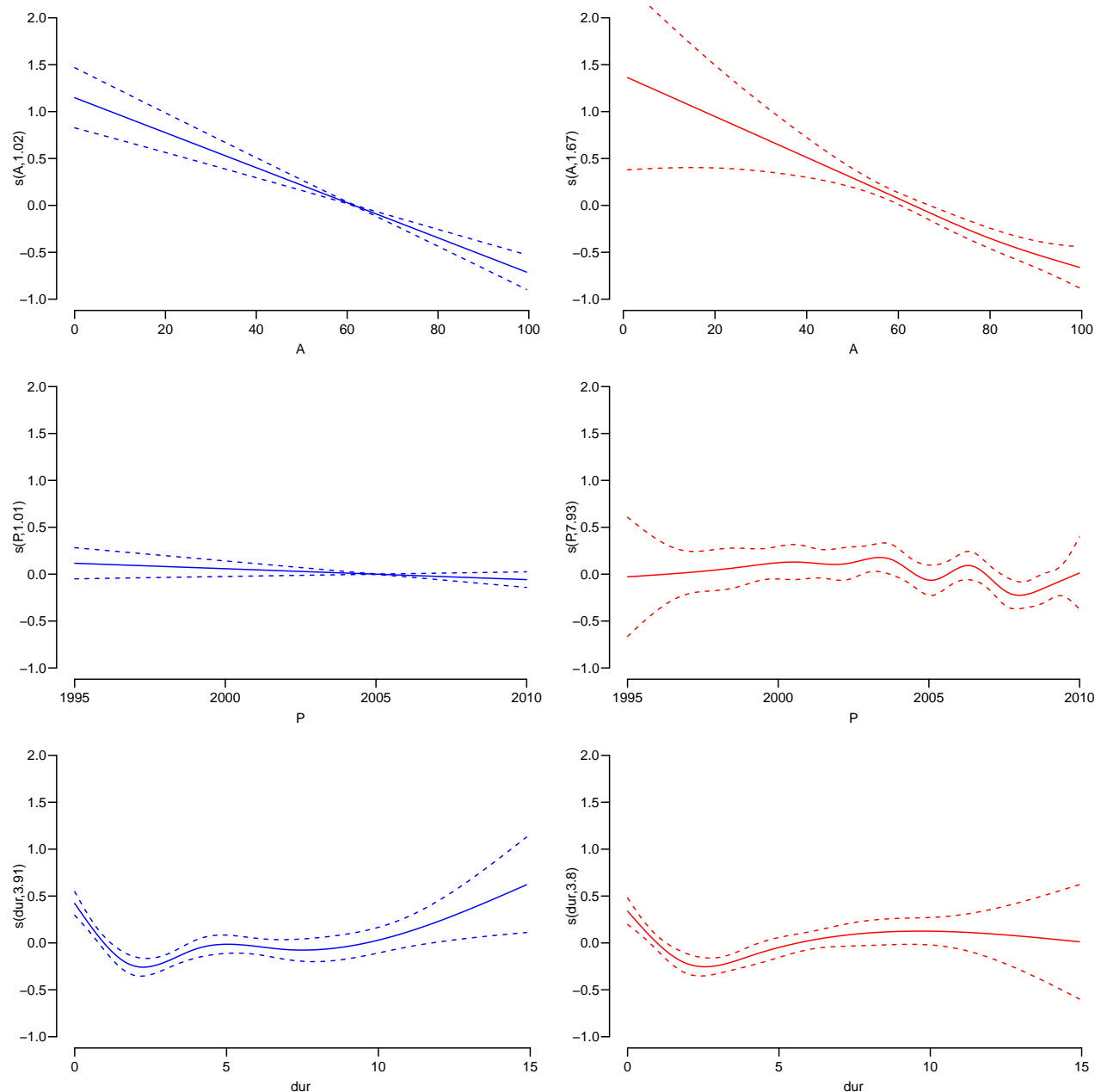


Figure 2.5: *Estimated effects of age, calendar time and duration on SMR — men on the left, women to the right.*

18. We then compute the predicted SMRs from the models for men and women diagnosed in ages 50, 60 and 70 in 1995 and 2005, respectively, and show them in plots side by side. We are going to make this type of plot for other models (well, pairs, for men and women) so we wrap it in a function:

```
plot(NA, xlim = c(50,80), ylim = c(0.5,5), log = "y",
 xlab = "Age", ylab = "SMR relative to total population")
abline(v = c(50,55,60,65,70), col = gray(0.8))
for(ip in c(1995,2005))
ip <- 2005
for(ia in c(50,60,70))
```



```

{
nd <- data.frame(A = ia + pts,
 P = ip + pts,
 dur = pts)
matshade(nd$A, rm <- ci.pred(Msmr, nd), col = "blue", lwd = 2)
matshade(nd$A, rf <- ci.pred(Fsmr, nd), col = "red", lwd = 2)
matshade(nd$A, ci.ratio(rm, rf), lwd = 2, col = gray(0.5))
}
abline(h = 1, lty = "55")

```

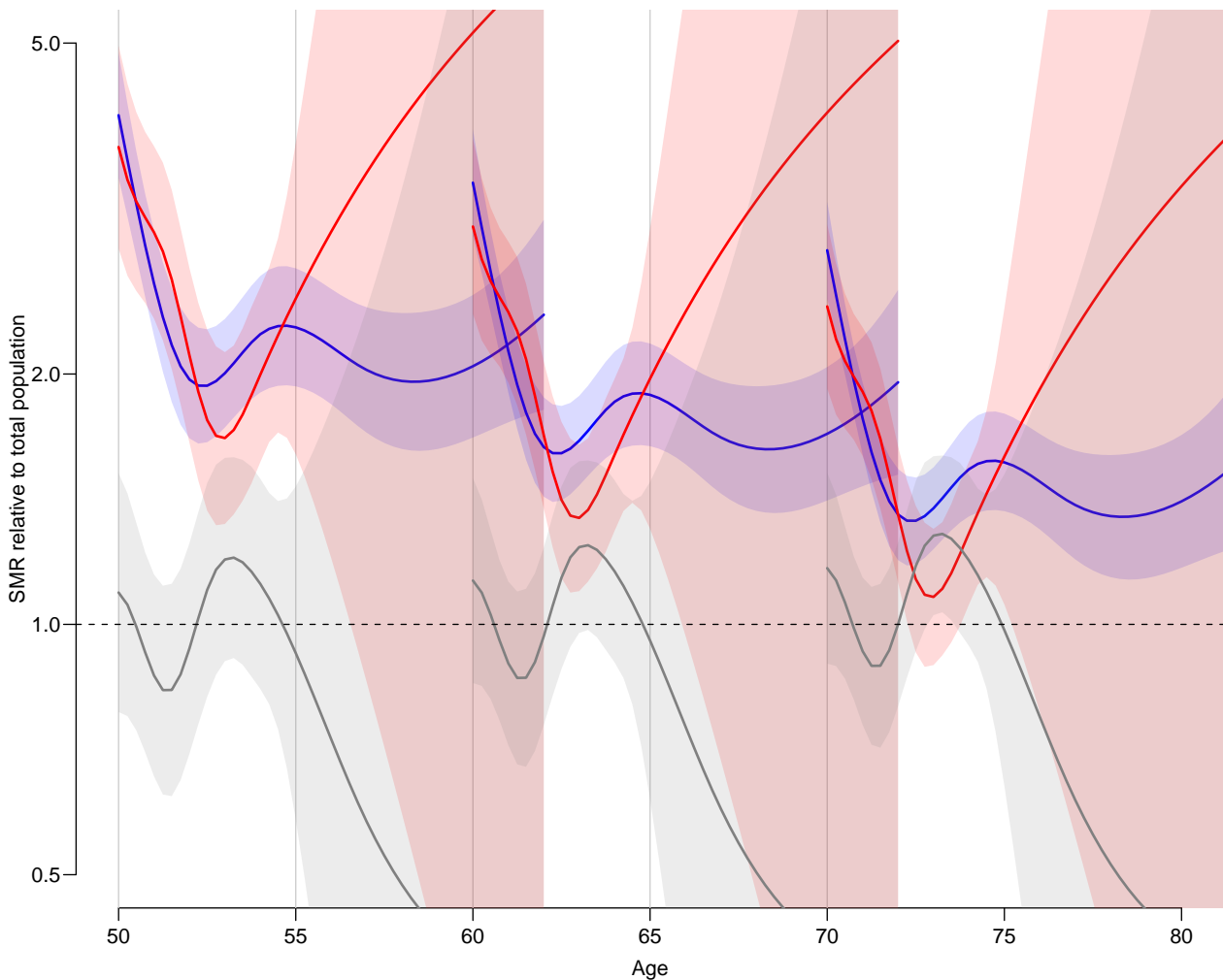


Figure 2.6: *Mortality rates for diabetes patients diagnosed 1995 and 2005 in ages 50, 60 and 70; as estimated by penalized splines. Men blue, women red.*

From figure 2.6 we see that as for mortality there is a clear peak at diagnosis and flattening after approximately 2 years. But also that the duration is possibly over-modeled. Finally there is no indication that the SMR is different for men and women.

19. It would be natural to simplify the model to one with a non-linear effect of duration and linear effects of age at diagnosis and calendar time, and moreover to squeeze the number of d.f. for the non-linear smooth term for duration:

```

Asmr <- gam(cbind(lex.Xst == "Dead", E) ~ sex +
 sex:I(A - 60) +
 sex:I(P - 2005) +
 s(dur, k = 5),
 family = poisreg,
 data = subset(SLr, E > 0))
summary(Asmr)

Family: poisson
Link function: log

Formula:
cbind(lex.Xst == "Dead", E) ~ sex + sex:I(A - 60) + sex:I(P -
 2005) + s(dur, k = 5)

Parametric coefficients:
 Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.802528 0.043472 18.461 < 2e-16 ***
sexF 0.009155 0.072211 0.127 0.8991
sexM:I(A - 60) -0.018857 0.002421 -7.789 6.75e-15 ***
sexF:I(A - 60) -0.019703 0.002696 -7.307 2.72e-13 ***
sexM:I(P - 2005) -0.013298 0.007936 -1.676 0.0938 .
sexF:I(P - 2005) -0.018566 0.008499 -2.185 0.0289 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Approximate significance of smooth terms:
 edf Ref.df Chi.sq p-value
s(dur) 3.82 3.98 59.52 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R-sq.(adj) = -0.000404 Deviance explained = 0.868%
UBRE = -0.8144 Scale est. = 1 n = 118432

round((ci.exp(Asmr, subset = "sex") - 1) * 100, 1)
 exp(Est.) 2.5% 97.5%
sexF 0.9 -12.4 16.3
sexM:I(A - 60) -1.9 -2.3 -1.4
sexF:I(A - 60) -2.0 -2.5 -1.4
sexM:I(P - 2005) -1.3 -2.8 0.2
sexF:I(P - 2005) -1.8 -3.5 -0.2

```

Thus the decrease in SMR per year of age is about 2% / year for both sexes and 1.3% per calendar year for men, but 1.8% per year for women.

The estimate of sex indicates that the SMR for 60 year old women in 2005 at duration 0 of DM (that is onset 20005) is about 3.6% larger than that of men, but nowhere near significantly so.

20. We can use the previous code to show the predicted mortality under this model.

```

plot(NA, xlim = c(50,80), ylim = c(0.8,5), log = "y",
 xlab = "Age", ylab = "SMR relative to total population")
abline(v = c(50,55,60,65,70), col = gray(0.8))
for(ip in c(1995,2005))
ip <- 2005

```

```

for(ia in c(50,55,60,65,70))
{
 nd <- data.frame(A = ia + pts,
 P = ip + pts,
 dur = pts)
 matshade(nd$A, rm <- ci.pred(Asmr, cbind(nd,sex = "M")), col = "blue", lwd = 2)
 matshade(nd$A, rf <- ci.pred(Asmr, cbind(nd,sex = "F")), col = "red", lwd = 2)
 matshade(nd$A, ci.ratio(rm, rf), lwd = 2, col = gray(0.5))
}
abline(h = 1, lty = "55")

```

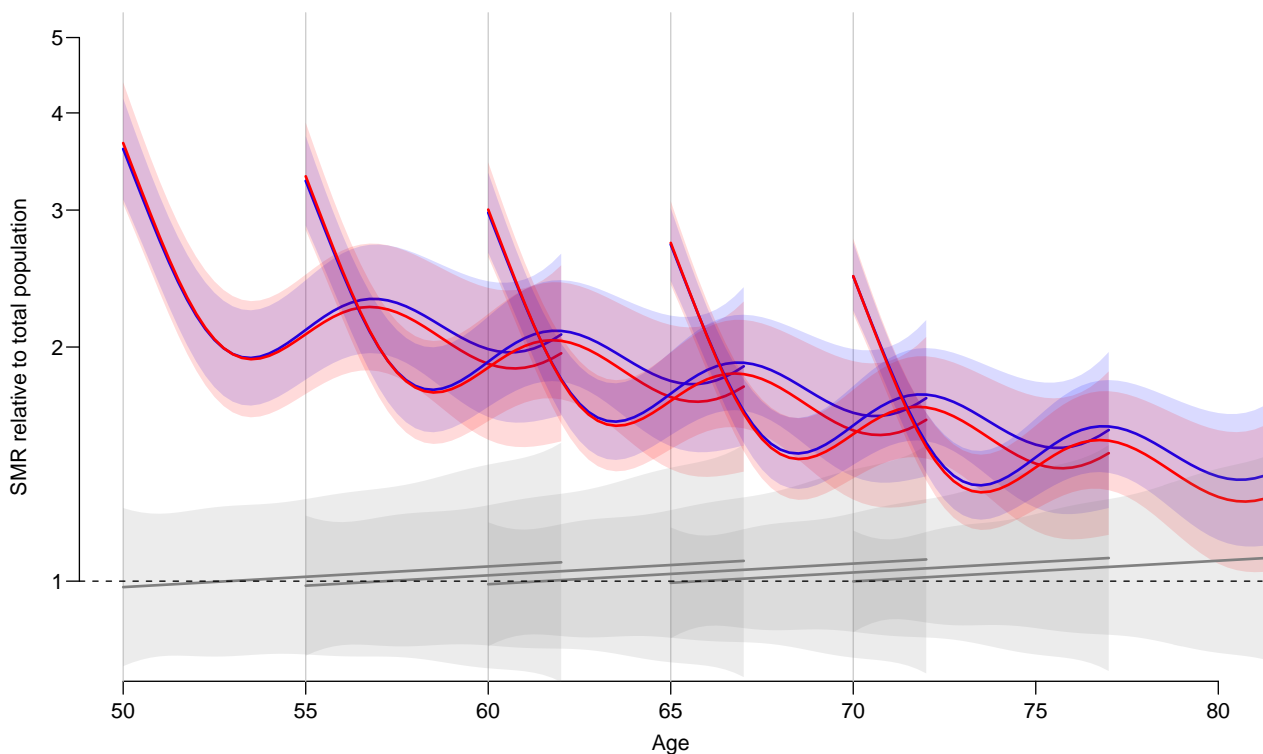


Figure 2.7: *Mortality rates for diabetes patients diagnosed 1995 and 2005 in ages 50, 60 and 70; as estimated by penalized splines. Men blue, women red.*

We see that there is absolutely no indication of difference between men and women, but also that the estimated effect of duration is not exactly credible.

## 2.14 Causal inference

### 2.14.1 Proper adjustment for confounding in regression models

The first exercise of this session will ask you to simulate some data according to pre-specified causal structure (don't take the particular example too seriously) and see how you should adjust the analysis to obtain correct estimates of the causal effects.

Suppose one is interested in the effect of beer-drinking on body weight. Let's *assume* that in addition to the potential effect of beer on weight, the following is true in reality:

- Men drink more beer than women
- Men have higher body weight than women
- People with higher body weight tend to have higher blood pressure
- Beer-drinking increases blood pressure

The task is to simulate a dataset in accordance with this model, and subsequently analyse it to see, whether the results would allow us to conclude the true association structure.

1. Sketch a causal graph (not necessarily with R) to see, how should one generate the data
2. Suppose the actual effect sizes are following:
  - The probability of beer-drinking is 0.2 for females and 0.7 for males
  - Men weigh on average 10kg more than women
  - One kg difference in body weight corresponds in average to 0.5mmHg difference in (systolic) blood pressures
  - Beer-drinking increases blood pressure by 10mmHg in average.
  - Beer-drinking has **no** effect on body weight

If you do want to draw the graph in R

```
> library(Epi)
> par(mar=c(0,0,0,0), cex=2)
> plot(NA, bty="n",xlim= c(40,100), ylim=c(0,80), xaxt="n", yaxt="n",
+ xlab="", ylab="") # create an empty plot with coordinates
> b<-0; w=12
> bb <- tbox("beer", 44, 40, w,w, col.txt="red" ,col.border=b)
> ww <- tbox("weight", 90, 40, w,w, col.txt="red" ,col.border=b)
> ss <- tbox("sex", 67, 70, w,w, col.txt="blue" ,col.border=b)
> bp <- tbox("BP", 67, 10, w,w, col.txt="blue" ,col.border=b)
> text(boxarr(bb, ww , col="red", lwd=3 ,gap= 4), "?", col="red", adj=c(0,-0.5))
> boxarr(bb, bp , col="blue", lwd=3)
> boxarr(ww, bp , col="blue", lwd=3)
> boxarr(ss, bb , col="blue", lwd=3)
> boxarr(ss, ww , col="blue", lwd=3)
```

*Following the algorithm from the lecture: remove BP and the corresponding arrows – it is not an ancestor of the exposure or outcome. Beer and weight are separated if sex is removed – thus one needs to adjust the analysis for sex*

The R commands to generate the data are:

```
> set.seed(02062017)
> bdat= data.frame(sex = c(rep(0,500),rep(1,500)))
> # a data frame with 500 females, 500 males
> bdat$beer <- rbinom(1000,1,0.2+0.5*bdat$sex)
> bdat$weight <- 60 + 10*bdat$sex + rnorm(1000,0,7)
> bdat$bp <- 110 + 0.5*bdat$weight + 10*bdat$beer + rnorm(1000,0,10)
```

3. Now fit the following models for body weight as dependent variable and beer-drinking as independent variable. Look, what is the estimated effect size:

- (a) Unadjusted (just simple linear regression)
- (b) Adjusted for sex
- (c) Adjusted for sex and blood pressure

```
> library(Epi)
> m1a<-lm(weight~beer, data=bdat)
> m2a<-lm(weight~beer+sex, data=bdat)
> m3a<-lm(weight~beer+sex+bp, data=bdat)
> ci.lin(m1a)
> ci.lin(m2a)
> ci.lin(m3a)
```

4. What would be the conclusions on the effect of beer on weight, based on the three models? Do they agree? Which (if any) of the models gives an unbiased estimate of the actual causal effect of interest?
5. How can the answer be seen from the graph?
6. Now change the data-generation algorithm so, that in fact beer-drinking does increase the body weight by 2kg. Look, what are the conclusions in the above models now. Thus the data is generated as before, but the weight variable is computed as:

```
> bdat$weight <- 60 + 10*bdat$sex + 2*bdat$beer + rnorm(1000,0,7)

> bdat$bp <- 110 +0.5*bdat$weight + 10*bdat$beer+ rnorm(1000,0,10) #
> m1b<-lm(weight~beer,data=bdat)
> m2b<-lm(weight~beer+sex,data=bdat)
> m3b<-lm(weight~beer+sex+bp,data=bdat)
> ci.lin(m1b)
> ci.lin(m2b) # the correct model
> ci.lin(m3b)
```

7. Suppose one is interested in the effect of beer-drinking on blood pressure instead, and is fitting a) an unadjusted model for blood pressure, with beer as an only covariate; b) a model with beer, weight and sex as covariates. Would either a) or b) give an unbiased estimate for the effect? (You may double-check whether the simulated data is consistent with your answer).

```
> m1bp<-lm(bp~beer,data=bdat)
> m2bp<-lm(bp~beer+weight,data=bdat)
> m3bp<-lm(bp~beer+weight+sex,data=bdat)
> ci.lin(m1bp)
> ci.lin(m2bp) # the correct model
> ci.lin(m3bp) # also correct!
```

### 2.14.2 Instrumental variables estimation, Mendelian randomization and assumptions

In the lecture slides it was shown that in a model for blood glucose level (associated with the risk of diabetes), both BMI and FTO genotype were significant. Seeing such result in a real dataset may misleadingly be interpreted as an evidence of a direct effect of FTO genotype on glucose. Conduct a simulation study to verify that one may see a significant genotype effect on outcome in such model if in fact the assumptions for Instrumental Variables estimation (Mendelian Randomization) are valid – genotype has a direct effect on the exposure only, whereas exposure-outcome association is confounded.

1. Start by generating the genotype variable as  $\text{Binomial}(2,p)$ , with  $p = 0.2$ :

```
> n <- 10000
> mrdat <- data.frame(G = rbinom(n,2,0.2))
> table(mrdat$G)
```

2. Also generate the confounder variable  $U$

```
> mrdat$U <- rnorm(n)
```

3. Generate a continuous (normally distributed) exposure variable  $BMI$  so that it depends on  $G$  and  $U$ . Check with linear regression, whether there is enough power to get significant parameter estimates. For instance:

```
> mrdat$BMI <- with(mrdat, 25 + 0.7*G + 2*U + rnorm(n))
```

4. Finally generate  $Y$  ("Blood glucose level") so that it depends on  $BMI$  and  $U$  (but not on  $G$ ).

```
> mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + rnorm(n,0,0.5))
```

5. Verify, that simple regression model for  $Y$ , with  $BMI$  as a covariate, results in a biased estimate of the causal effect (parameter estimate is different from what was generated)

```
> mxy<-lm(Y ~ BMI, data=mrdat)
> ci.lin(mxy)
```

How different is the estimate from 0.1?

6. Estimate a regression model for  $Y$  with two covariates,  $G$  and  $BMI$ . Do you see a significant effect of  $G$ ? Could you explain analytically, why one may see a significant parameter estimate for  $G$  there?

```
> mxyg<-lm(Y ~ G + BMI, data=mrdat)
> ci.lin(mxyg)
```

7. Find an IV (instrumental variables) estimate, using  $G$  as an instrument, by following the algorithm in the lecture notes (use two linear models and find a ratio of the parameter estimates). Does the estimate get closer to the generated effect size?

```
> mgx<-lm(BMI ~ G, data=mrdat)
> ci.lin(mgx) # check the instrument effect
> bgx<-mgx$coef[2] # save the 2nd coefficient (coef of G)
> mgy<-lm(Y ~ G, data=mrdat)
> ci.lin(mgy)
> bgy<-mgy$coef[2]
> causeff <- bgy/bgx
> causeff # closer to 0.1?
```

8. A proper simulation study would require the analysis to be run several times, to see the extent of variability in the parameter estimates. A simple way to do it here would be using a `for`-loop. Modify the code as follows (exactly the same commands as executed so far, adding a few lines of code to the beginning and to the end):

```
> n <- 10000
> # initializing simulations:
> # 30 simulations (change it, if you want more):
> nsim<-30
> mr<-rep(NA,nsim) # empty vector for the outcome parameters
> for (i in 1:nsim) { # start the loop
+ ### Exactly the same commands as before:
+ mrdat <- data.frame(G = rbinom(n,2,0.2))
+ mrdat$U <- rnorm(n)
+ mrdat$BMI <- with(mrdat, 25 + 0.7*G + 2*U + rnorm(n))
+ mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + rnorm(n,0,0.5))
+ mgx<-lm(BMI ~ G, data=mrdat)
+ bgx<-mgx$coef[2]
+ mgy<-lm(Y ~ G, data=mrdat)
+ bgy<-mgy$coef[2]
+ # Save the i'th parameter estimate:
+ mr[i]<-bgy/bgx
+ } # end the loop
```

Now look at the distribution of the parameter estimate:

```
> summary(mr)
```

9. (*optional*) Change the code of simulations so that the assumptions are violated: add a weak direct effect of the genotype  $G$  to the equation that generates  $Y$ :

```
> mrdat$Y <- with(mrdat, 3 + 0.1*BMI - 1.5*U + 0.05*G + rnorm(n,0,0.5))
```

Repeat the simulation study to see, what is the bias in the average estimated causal effect of  $BMI$  on  $Y$ .

10. (*optional*) Using library `sem` and function `tsls`, obtain a two-stage least squares estimate for the causal effect. Do you get the same estimate as before?

```
> library(sem)
> summary(tsls(Y ~ BMI, ~G, data=mrdat))
```

**Why are simulation exercises useful for causal inference?**

If we simulate the data, we know the data-generating mechanism and the “true” causal effects. So this is a way to check, whether an analysis approach will lead to estimates that correspond to what is generated. One could expect to see similar phenomena in real data analysis, if the data-generation mechanism is similar to what was used in simulations.



## 2.15 Causal inference 2: Model-based estimation of causal estimands

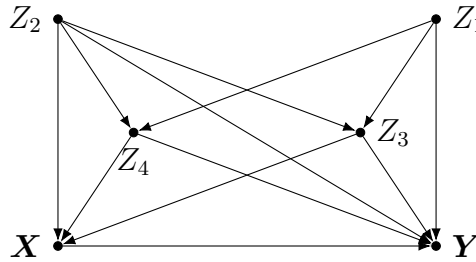
Sources of inspiration: [Luque Fernandez, M.A. et al. \(2018\)](#) *Stat Med* 2018;37(16):2530-2546 and

[Smith et al. \(2022\)](#) *Stat Med* 2022;41(2):407-432.

We shall illustrate with simulated data the estimation of causal effects of a binary exposure  $X$  when the outcome  $Y$  is also binary, and there is a set of four covariates  $Z = (Z_1, Z_2, Z_3, Z_4)$ . As a background story, we imagine a population of cancer patients, in whom the variables and the assumed marginal distributions of the covariates are

- $X$  = treatment; 1: radiotherapy only, 0: radiotherapy + chemotherapy,
- $Y$  = death during one year after diagnosis of cancer,
- $Z_1$  = sex; 0: man, 1: woman;  $Z_1 \sim \text{Bern}(0.5)$ ,
- $Z_2$  = age group 0: “young”, 1: “old”;  $Z_2 \sim \text{Bern}(0.65)$ ,
- $Z_3$  = stage of cancer; 4 classes;  $Z_3 \sim \text{DiscUnif}(1, \dots, 4)$ ,
- $Z_4$  = comorbidity score; 5 classes;  $Z_4 \sim \text{DiscUnif}(1, \dots, 5)$ .

For simplicity, covariates  $Z_3$  and  $Z_4$  are treated as continuous variables in the models. The assumed causal diagram is shown below.



For more generic notation, the probabilities of  $Y = 1$  will be expressed as expectations, e.g.  $E(Y^{X=x}) = P(Y^{X=x} = 1)$  and  $E(Y|X = x, Z = z) = P(Y = 1|X = x, Z = z)$ , where  $Z$  is the vector of relevant covariates. The same principle is applied in expressing the conditional probability of  $X = 1$  given  $Z = z$ . The fitted or predicted probabilities of  $Y = 1$  are denoted as fitted  $\hat{Y}$  or predicted values  $\tilde{Y}$  of  $Y$  with pertinent subscripts and/or superscripts. Both  $X$  and  $Y$  are modelled by logistic regression. The expit-function or inverse of the logit function is defined:  $\text{expit}(u) = 1/(1 + e^{-u})$ ,  $u \in \mathbb{R}$ . This is equal to the cumulative distribution function of the standard logistic distribution, the values of which are returned in R by `plogis(u)`. The R function that returns values of the logit-function is `qlogis()`.

The true model assumed for the dependence of exposure  $X$  on covariates:

$$E(X|Z_1 = z_1, \dots, Z_4 = z_4) = \text{expit}(-5 + 0.05z_2 + 0.25z_3 + 0.5z_4 + 0.4z_2z_4).$$

The assumed true model for the outcome is

$$E(Y|X = x, Z_1 = z_1, \dots, Z_4 = z_4) = \text{expit}(-1 + x - 0.1z_1 + 0.35z_2 + 0.25z_3 + 0.20z_4 + 0.15z_2z_4)$$

Note that  $X$  does not depend on  $Z_1$ , and that in both models there is a product term  $Z_2Z_4$ , which appears weaker for the outcome model.

### 2.15.1 Control of confounding

1. Based on inspection of the causal diagram, can you identify a proper subset from the four covariates, which would be sufficient to block all backdoor paths between  $X$  and  $Y$  and thus remove confounding?
2. Even if such a minimal sufficient set is found in item (a), why could it still be worth while to include all covariates when modelling the outcome?

### 2.15.2 Generation of target population and true models

1. Load the necessary packages.

```
> library(Epi)
> library(stdReg)
> library(PWeight)
> library(SuperLearner)
> library(tmle)
```

2. Define the R-functions for the true outcome model and the true exposure model.

```
> EX <- function(z2, z3, z4) {
+ plogis(-5 + 0.05*z2 + 0.25*z3 + 0.5*z4 + 0.4*z2*z4) }
> EY <- function(x, z1, z2, z3, z4) {
+ plogis(-1 + x - 0.1*z1 + 0.35*z2 + 0.25*z3 +
+ 0.20*z4 + 0.15*z2*z4) }
```

3. Define the function for the generation of data based on the given assumptions

```
> genData <- function(N) {
+ z1 <- rbinom(N, size=1, prob=0.5) # Bern(0.5)
+ z2 <- rbinom(N, size=1, prob=0.65) # Bern(0.65)
+ z3 <- trunc(runif(N, min=1, max=5), digits=0) # DiscUnif(1,4)
+ z4 <- trunc(runif(N, min=1, max=6), digits=0) # DiscUnif(1,5)
+ x <- rbinom(N, size=1, prob=EX(z2, z3, z4))
+ y <- rbinom(N, size=1, prob=EY(x, z1, z2, z3, z4))
+ data.frame(z1, z2, z3, z4, x, y)
+ }
```

4. Generate a data frame `dd` for a big target population of 500000 subjects

```
> N <- 500000
> set.seed(7777)
> dd <- genData(N)
```

### 2.15.3 Factual and counterfactual risks – associational and causal contrasts

1. Compute the factual risks of death for the two exposure groups

$$E(Y|X = x) = P(Y = 1|X = x) = \frac{P(Y = 1 \& X = x)}{P(X = x)}, \quad x = 0, 1,$$

in the whole target population, as well as their associational contrasts: risk difference, risk ratio, and odds ratio. Before that define a useful function

```
> Contr <- function(mu1, mu0) {
+ RD <- mu1 - mu0
+ RR <- mu1/mu0
+ OR <- (mu1/(1-mu1)) / (mu0/(1-mu0))
+ return(c(mu1, mu0, RD=RD, RR=RR, OR=OR))
+ }
> Ey1 <- with(dd, sum(y==1 & x==1)/sum(x==1))
> Ey0 <- with(dd, sum(y==1 & x==0)/sum(x==0))
> round(Contr(Ey1, Ey0), 4)
```

```
 RD RR OR
0.8949 0.6288 0.2661 1.4232 5.0286
```

How much bigger is the risk of death of those exposed to radiotherapy only as compared with those receiving chemotherapy, too?

2. Compute the counterfactual risks of death  $E(Y_i^{X_i=x}) = P(Y_i^{X_i=x} = 1) = \pi_i^{X_i=x}$  for each individual under the alternative treatments or exposure values  $x = 0, 1$  with given covariate values, the average or overall counterfactual risks  $E(Y^{X=1}) = \pi^1$  and  $E(Y^{X=0}) = \pi^0$  in the population, and the true marginal causal contrasts for the effect of  $X$ :

$$\begin{aligned} \text{RD} &= E(Y^{X=1}) - E(Y^{X=0}), & \text{RR} &= E(Y^{X=1})/E(Y^{X=0}), \\ \text{OR} &= \frac{E(Y^{X=1})/[1 - E(Y^{X=1})]}{E(Y^{X=0})/[1 - E(Y^{X=0})]} \end{aligned}$$

```
> dd <- transform(dd, EY1.ind = EY(1, z1, z2, z3, z4),
+ EY0.ind = EY(0, z1, z2, z3, z4))
> EY1 <- mean(dd$EY1.ind)
> EY0 <- mean(dd$EY0.ind)
> round(Contr(EY1, EY0), 4)
```

```
 RD RR OR
0.8273 0.6530 0.1743 1.2670 2.5462
```

3. Compare the associational contrasts in item (a) with the causal contrasts in item (b). What do you conclude about confoundedness of the associational contrasts?

### 2.15.4 Outcome modelling and estimation of causal contrasts by g-formula

As the first approach for estimating causal contrast of interest we apply the method of standardization or g-formula. Is based on a hopefully realistic enough model for  $E(Y|X = x, Z = z)$ , i.e. how the probability of outcome is expected to depend on the exposure variable  $X$  and on a sufficient set  $Z$  of confounders. The counterfactual risks are marginal expectations of the above quantities, standardized over the joint distribution of the confounders  $Z$  in the target population.

$$E(Y^{X=x}) = E_Z[E(Y|X = x, Z)] = \int E(Y|X = x, Z = z)dF_Z(z), \quad x = 0, 1.$$

1. Assume now a – slightly misspecified – model  $mY$  for the outcome, which contains only main effect terms of the explanatory variables:

$$\pi_i = E(Y_i|X_i = x_i, Z_{i1} = z_{i1}, \dots, Z_{i4} = z_{i4}) = \text{expit} \left( \beta_0 + \delta x_i + \sum_{j=1}^4 \beta_j z_{ij} \right)$$

Fit this model for the whole population in order to have an accurate estimate of the possible bias due to misspecification of the outcome model

```
> mY <- glm(y ~ x + z1 + z2 + z3 + z4, family = binomial, data = dd)
> round(ci.lin(mY, Exp=TRUE)[, c(1,5)], 3)
```

|             | Estimate | exp(Est.) |
|-------------|----------|-----------|
| (Intercept) | -1.240   | 0.289     |
| x           | 1.052    | 2.863     |
| z1          | -0.095   | 0.909     |
| z2          | 0.767    | 2.153     |
| z3          | 0.250    | 1.284     |
| z4          | 0.279    | 1.322     |

There is not much idea in looking at the standard errors or confidence intervals in such a big target population.

2. For each subject  $i$ , compute the fitted individual risk  $\hat{Y}_i$  as well as the predicted counterfactual risks  $\tilde{Y}_i^{X_i=x}$  for both exposure levels  $x = 0, 1$  separately, keeping the individual values of the  $Z$ -variables as they are.

```
> dd$yh <- predict(mY, type = "response")
> dd$yp1 <- predict(mY, newdata=data.frame(x=rep(1,N),
+ dd[,c("z1","z2","z3","z4")]), type = "response")
> dd$yp0 <- predict(mY, newdata=data.frame(x=rep(0,N),
+ dd[,c("z1","z2","z3","z4")]), type = "response")
```

3. Applying the method of standardization or g-formula compute the point estimates

$$\hat{E}_g(Y^{X=x}) = \frac{1}{n} \sum_{i=1}^n \tilde{Y}_i^{X_i=x}, \quad x = 0, 1.$$

of the two counterfactual risks  $E(Y^{X=1}) = \pi^1$  and  $E(Y^{X=0}) = \pi^0$  as well as the marginal causal contrasts

```
> EY1.g <- mean(dd$yp1)
> EY0.g <- mean(dd$yp0)
> round(Contr(EY1.g, EY0.g), 4)

 RD RR OR
0.8330 0.6508 0.1822 1.2800 2.6763
```

The expectations  $E_Z[E(X = x, Z)]$  taken over the joint distribution of the confounders  $Z$  are empirically estimated from the data by simply computing the arithmetic means of the individually predicted values  $\tilde{Y}_i^{X_i=x}$  of the outcome for the two exposure levels.

Compare the estimated contrast with the true ones in item 3(b) above. How big was the bias due to slight misspecification of the outcome model? Compare in particular the estimate of the marginal OR here with the conditional OR obtained in item (a) from the pertinent coefficient in the logistic model. Which one is closer to 1?

4. Perform the same calculations using the tools in package `stdReg` (see [Sjölander 2016](#))

```
> mY.std <- stdGlm(fit=mY, data=dd, X="x")
> summary(mY.std)

Formula: y ~ x + z1 + z2 + z3 + z4
Family: binomial
Link function: logit
Exposure: x

 Estimate Std. Error lower 0.95 upper 0.95
0 0.651 0.000733 0.649 0.652
1 0.833 0.001562 0.830 0.836

> round(summary(mY.std, contrast = "difference", reference=0)$est.table, 4)

 Estimate Std. Error lower 0.95 upper 0.95
0 0.0000 0.0000 0.0000 0.0000
1 0.1822 0.0017 0.1788 0.1856

> round(summary(mY.std, contrast = "ratio", reference=0)$est.table, 4)

 Estimate Std. Error lower 0.95 upper 0.95
0 1.00 0.0000 1.0000 1.0000
1 1.28 0.0028 1.2745 1.2855

> round(summary(mY.std, transform="odds",
+ contrast = "ratio", reference=0)$est.table, 4)

 Estimate Std. Error lower 0.95 upper 0.95
0 1.0000 0.0000 1.0000 1.0000
1 2.6763 0.0315 2.6146 2.7379
```

Check that you got the same point estimates as in the previous item. Again, the confidence intervals are not very meaningful when analysing the data covering the whole big target population. Of course, when applied to sample data they are relevant. In `stdReg` package, the standard errors are obtained by the multivariate delta method built upon M-estimation and robust sandwich estimator of the pertinent covariance matrix, and approximate confidence intervals are derived from these in the usual way.

5. If we are interested in the causal contrasts describing the effect of exposure among those exposed (like ATT), the relevant factual and counterfactual risks in that subset are

$$\pi_1^1 = E(Y^{X=1}|X = 1) = E(Y|X = 1) = \pi_1,$$

$$\pi_1^0 = E(Y^{X=0}|X = 1) = \sum_{X_i=1} E(Y|X = 0, Z = z)P(Z = z|X = 1)$$

We are thus making an “observed vs. expected” comparison, in which the  $z$ -specific risks in the unexposed are weighted by the distribution of  $Z$  in the exposed subset of the target population. The risks and their contrasts are estimated from the fit of the outcome model:

```
> EY1att.g <- mean(subset(dd, x==1)$yp1)
> EY0att.g <- mean(subset(dd, x==1)$yp0)
> round(Contr(EY1att.g, EY0att.g), 4)
```

|        |        |        | RD     | RR     | OR |
|--------|--------|--------|--------|--------|----|
| 0.8949 | 0.7560 | 0.1389 | 1.1837 | 2.7488 |    |

Compare the results here with those for the whole target population. What do you observe? Any guess about the causal effect of exposure among the unexposed; is it bigger or smaller than among the exposed or among the whole population?

6. Incidentally, the true causal contrasts among the exposed based on the true model are similarly obtained from the quantities in item 3(b) above:

```
> EY1att <- mean(subset(dd, x==1)$EY1.ind)
> EY0att <- mean(subset(dd, x==1)$EY0.ind)
> round(Contr(EY1att, EY0att), 4)
```

|        |        |        | RD     | RR     | OR |
|--------|--------|--------|--------|--------|----|
| 0.8955 | 0.7680 | 0.1275 | 1.1661 | 2.5896 |    |

Compare the estimates in the previous item with the true values obtained here.

### 2.15.5 Inverse probability weighting (IPW) by propensity scores, and augmented IPW

The next method is based on weighting each individual observation by the inverse of the probability of belonging to that particular exposure group, which was realized, this probability being predicted by determinants of exposure.

1. Fit first a model for the exposure including main effects of the  $Z$ -variables only.

$$p_i = E(X_i|Z_{1i} = z_{1i}, \dots, Z_{4i} = z_{4i}) = \text{expit}(\gamma_0 + \gamma_1 z_{1i} + \gamma_2 z_{2i} + \gamma_3 z_{3i} + \gamma_4 z_{4i}), \quad i = 1, \dots, N$$

```
> mX <- glm(x ~ z1 + z2 + z3 + z4,
+ family = binomial(link=logit), data = dd)
> round(ci.lin(mX, Exp=TRUE)[, c(1, 5)], 4)
```

```

 Estimate exp(Est.)
(Intercept) -6.3031 0.0018
z1 -0.0161 0.9840
z2 1.6260 5.0833
z3 0.2391 1.2702
z4 0.8369 2.3093

```

2. Extract the propensity scores, i.e. fitted probabilities of belonging to exposure group 1:  $PS_i = \hat{p}_i$ , and compare their distribution between the exposure groups.

```

> dd$PS = predict(mX, type = "response")
> summary(dd$PS)

 Min. 1st Qu. Median Mean 3rd Qu. Max.
0.005256 0.041532 0.112765 0.172440 0.248554 0.613993

> with(subset(dd, x==0), plot(density(PS), lty=2))
> with(subset(dd, x==1), lines(density(PS), lty=1))

```

How different are the distributions? Are they sufficiently overlapping?

3. Compute the weights  $W_i = 1/PS_i$ , when  $X_i = 1$ , and  $W_i = 1/(1 - PS_i)$ , when  $X_i = 0$ . Look at the sum as well as the distribution summary of the weights in the exposure groups. The sum of weights should be close to  $n$  in both groups.

```

> dd$w <- ifelse(dd$x==1, 1/dd$PS, 1/(1-dd$PS))
> with(dd, tapply(w, x, sum))

 0 1
498880.5 565237.5

```

4. Compute now the weighted estimates of the counterfactual risks for both exposure categories

$$\hat{E}_w(Y^{X=x}) = \frac{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i Y_i}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} = \frac{\sum_{X_i=x} W_i Y_i}{\sum_{X_i=x} W_i}, \quad x = 0, 1,$$

and their causal contrasts, for instance

$$\widehat{RD}_w = \hat{E}_w(Y^{X=1}) - \hat{E}_w(Y^{X=0}) = \frac{\sum_{i=1}^n X_i W_i Y_i}{\sum_{i=1}^n X_i W_i} - \frac{\sum_{i=1}^n (1 - X_i) W_i Y_i}{\sum_{i=1}^n (1 - X_i) W_i}$$

```

> EY1.w <- sum(dd$x * dd$w * dd$y) / sum(dd$x * dd$w)
> EY0.w <- sum((1-dd$x) * dd$w * dd$y) / sum((1-dd$x) * dd$w)
> round(Contr(EY1.w, EY0.w), 4)

```

```

 RD RR OR
0.8037 0.6519 0.1518 1.2329 2.1868

```

The estimate seems to be downward biased. Could this be so, because of ignoring the relatively strong product term effect of  $Z_2$  and  $Z_4$ ?

- Let us attempt to correct the estimates by a double robust approach called augmented IPW estimation (AIPW), which combines the g-formula and the IPW approach. The AIPW-estimator can be expressed in two ways: either an IPW-corrected g-formula estimator, or a g-corrected IPW-estimator.

$$\begin{aligned}\widehat{E}_a(Y^{X=x}) &= \widehat{E}_g(Y^{X=x}) + \frac{1}{n} \sum_{i=1}^n \frac{\mathbf{1}_{\{X_i=x\}} W_i (Y_i - \widetilde{Y}_i^{X_i=x})}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} \\ &= \widehat{E}_w(Y^{X=x}) - \frac{1}{n} \sum_{i=1}^n \left[ \frac{\mathbf{1}_{\{X_i=x\}} W_i}{\sum_{i=1}^n \mathbf{1}_{\{X_i=x\}} W_i} - 1 \right] \widetilde{Y}_i^{X_i=x}.\end{aligned}$$

```
> EY1.a <- EY1.g + mean(dd$x *(dd$y - dd$yp1)*dd$w/sum(dd$x*dd$w))
> ## or EY1.w - mean(((dd$x*dd$w /sum(dd$x*dd$w)) - 1)*dd$yp1)
> EY0.a <- EY0.g + mean((1 - dd$x)*(dd$y - dd$yp0)*dd$w/sum((1-dd$x)*dd$w))
> ## or EY0.w - mean((((1-dd$x)*dd$w/sum((1-dd$x)*dd$w)) - 1)*dd$yp0)
> round(Contr(EY1.a, EY0.a), 4)
```

|  | RD     | RR     | OR     |
|--|--------|--------|--------|
|  | 0.8330 | 0.6508 | 0.1822 |
|  | 1.2800 | 2.6763 |        |

Compare these results with those obtained by g-formula and by non-augmented IPW method. Was augmentation successful?

### 2.15.6 Improving IPW estimation and using R package PSweight

We now try to improve IPW-estimation by a richer exposure model. In computations we shall utilize the R package `PSweight` (see [PSweight vignette](#)).

- First, we compute the weights from a more flexible exposure model which contains all pairwise product terms of the parents of  $X$ . According to the causal diagram,  $Z_1$  is not in that subset, so it is left out. The exposure model is specified and the weights are obtained as follows.

```
> mX2 <- glm(x ~ (z2 + z3 + z4)^2, family=binomial, data=dd)
> round(ci.lin(mX2, Exp=TRUE)[, c(1,5)], 3)
```

|             | Estimate | exp(Est.) |
|-------------|----------|-----------|
| (Intercept) | -5.085   | 0.006     |
| z2          | 0.143    | 1.154     |
| z3          | 0.243    | 1.275     |
| z4          | 0.527    | 1.693     |
| z2:z3       | -0.003   | 0.997     |
| z2:z4       | 0.376    | 1.456     |
| z3:z4       | 0.001    | 1.001     |

```
> psw <- SumStat(ps.formula=mX2$formula, data=dd,
+ weight=c("IPW", "treated", "overlap"))
> dd$PS2 <- psw$propensity[, 2] # propensity scores extracted
> plot(density(dd$PS2[dd$x==0]), lty=2)
> lines(density(dd$PS2[dd$x==1]), lty=1)
```



Note that apart from ordinary IPW, other types of weights can also be obtained.

These are relevant when estimating other causal contrasts, like “average treatment effect among the treated” (ATT) and “average treatment effect in the overlap (or equipoise) population” (ATO).

2. **PSweight** includes some useful tools to examine the properties of the distribution and to check the balance of the propensity scores, for instance

```
> plot(psw, type="balance", metric="PSD")
```

It is desirable that the horizontal values of these measures for given weights are less than 0.1.

3. Estimation and reporting of the causal contrasts. For relative contrasts, the summary method provides the results on the log-scale.

```
> ipwest <- PSweight(ps.formula=mX2, yname="y", data = dd, weight= "IPW")
> ipwest
```

```
Original group value: 0, 1
```

```
Point estimate:
0.6526, 0.8255
```

```
> summary(ipwest)
```

```
Closed-form inference:
```

```
Original group value: 0, 1
```

```
Contrast:
```

```
 0 1
```

```
Contrast 1 -1 1
```

```
 Estimate Std.Error lwr upr Pr(>|z|)
Contrast 1 0.1729179 0.0025636 0.1678934 0.17794 < 2.2e-16 ***
```

```

```

```
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
> (logRR.ipw <- summary(ipwest, type="RR"))
```

```
Closed-form inference:
```

```
Inference in log scale:
```

```
Original group value: 0, 1
```

```
Contrast:
```

```
 0 1
```

```
Contrast 1 -1 1
```

```
 Estimate Std.Error lwr upr Pr(>|z|)
Contrast 1 0.2350512 0.0031789 0.2288207 0.24128 < 2.2e-16 ***
```

```

```

```
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
> round(exp(logRR.ipw$estimates[c(1,4,5)]), 3)
```

```
[1] 1.265 1.257 1.273
```

```
> round(exp(summary(ipwest, type="OR")$estimates[c(1,4,5)]), 3)
[1] 2.519 2.434 2.606
```

Compare these with the previous IPW estimate and the AIPW estimate as well as the true values. Have we obtained nearly unbiased results?

The standard errors provided by `PSweight` are by default based on the empirical sandwich covariance matrix and application of delta method as appropriate.

Bootstrapping is also possible but is computationally very intensive and is recommended to be used only in relatively small samples.

4. If we are interested in the effect of exposure among the exposed (like ATT) then the weights are  $W_i = 1$  for the exposed and  $W_i = PS_i / (1 - PS_i)$  for the unexposed. Call again `PSweight` but with another choice of weight:

```
> psatt <- PSweight(ps.formula=mX2, yname="y", data = dd, weight= "treated")
> psatt

Original group value: 0, 1
Treatment group value: 1

Point estimate:
0.7667, 0.8949

> round(summary(psatt)$estimates[1], 4)
[1] 0.1282

> round(exp(summary(psatt,type="RR")$estimates[1]), 3)
[1] 1.167

> round(exp(summary(psatt, type="OR")$estimates[1]), 3)
[1] 2.592
```

Compare the results here with those obtained by g-formula in item 4(e) and with the true contrasts in item 4(f) above.

### 2.15.7 Targeted maximum likelihood estimation (TMLE)

We now consider now another double robust approach, known as targeted maximum likelihood estimation (TMLE). It also corrects the estimator obtained from the outcome model by elements that are derived from the exposure model.

1. The first step is to utilize the propensity scores obtained above and define the so called clever covariates

```
> dd$H1 <- dd$x / dd$PS2
> dd$H0 <- (1-dd$x) / (1 - dd$PS2)
```

2. Then, a working model is fitted for the outcome, in which the clever covariates are explanatory variables, but the model also includes the previously fitted linear predictor  $\hat{\eta}_i = \text{logit}(\hat{Y}_i)$  from the original outcome model `mY` as an offset term.

```
> epsmod <- glm(y ~ -1 + H0 + H1 + offset(qlogis(yh)),
+ family = binomial(link=logit), data=dd)
> eps <- coef(epsmod)
> eps
```

```
 H0 H1
0.007197951 -0.002859654
```

3. The logit-transformed predicted values  $\tilde{Y}_i^{X_i=1}$  and  $\tilde{Y}_i^{X_i=0}$  of counterfactual individual risks from the original outcome model are now corrected by the estimated coefficients of the clever covariates, and the corrected predictions are returned to the original scale.

```
> yp0.H <- plogis(qlogis(dd$yp0) + eps[1] / (1 - dd$PS2))
> yp1.H <- plogis(qlogis(dd$yp1) + eps[2] / dd$PS2)
```

Estimates of the causal contrasts:

4. 

```
> EY0.t <- mean(yp0.H)
> EY1.t <- mean(yp1.H)
> round(Contr(EY1.t, EY0.t), 4)
```
- ```
           RD           RR           OR
0.8246 0.6526 0.1720 1.2635 2.5020
```

Compare these with previous results and with the true values.

2.15.8 TMLE with SuperLearner

Let us finally apply some fashionable tools of statistical learning, aka “machine learning”, using the package **SuperLearner** to fit flexible models for both exposure and outcome. As this method is computationally much more demanding, we illustrate its use by a sample of 2000 subjects only.

1. A simple random sample of $n = 2000$ is drawn from the population.

```
> set.seed(7622)
> n <- 2000
> sampind <- sample(N, n)
> samp <- dd[sampind, ]
```

2. The algorithms to be used in this exercise are chosen

```
> SL.library <- c("SL.glm" , "SL.step", "SL.step.interaction",
+   "SL.glm.interaction", "SL.gam",
+   "SL.randomForest", "SL.rpart")
```

3. Function `tmle()` computes estimates of the causal contrasts of interest. Argument **A** is for the exposure variable, and argument **W** contains the confounders. – The run can take a while ...

```
> tmlest <- tmle(Y = samp$y, A = samp$x, W = samp[,c("z1", "z2", "z3", "z4")],
+               family = "binomial", Q.SL.library = SL.library,
+               g.SL.library = SL.library)
> summary(tmlest)
```

Initial estimation of Q

Procedure: cv-SuperLearner, ensemble

Model:

$Y \sim \text{SL.glm_All} + \text{SL.step_All} + \text{SL.step.interaction_All} + \text{SL.glm.interact}$

Coefficients:

SL.glm_All	0.147156
SL.step_All	0.3536965
SL.step.interaction_All	0.02141815
SL.glm.interaction_All	0.4740045
SL.gam_All	0
SL.randomForest_All	0.003724871
SL.rpart_All	0

Cross-validated pseudo R squared : 0.0922

Estimation of g (treatment mechanism)

Procedure: SuperLearner, ensemble

Empirical AUC = 0.8122

Model:

$A \sim \text{SL.glm_All} + \text{SL.step_All} + \text{SL.step.interaction_All} + \text{SL.glm.interact}$

Coefficients:

SL.glm_All	0.29927
SL.step_All	0
SL.step.interaction_All	0.6456851
SL.glm.interaction_All	0
SL.gam_All	0
SL.randomForest_All	0.05504491
SL.rpart_All	0

Estimation of g.Z (intermediate variable assignment mechanism)

Procedure: No intermediate variable

Estimation of g.Delta (missingness mechanism)

Procedure: No missingness, ensemble

Bounds on g: (0.0147, 1)

Bounds on g for ATT/ATE: (0.0147, 0.9853)

Additive Effect

Parameter Estimate:	0.1781
Estimated Variance:	0.0014827
p-value:	3.7392e-06
95% Conf Interval:	(0.10263, 0.25357)

Additive Effect among the Treated

Parameter Estimate:	0.13505
Estimated Variance:	0.00050661
p-value:	1.9726e-09
95% Conf Interval:	(0.090934, 0.17917)

Additive Effect among the Controls

```

Parameter Estimate: 0.18572
Estimated Variance: 0.0018725
p-value: 1.7713e-05
95% Conf Interval: (0.10091, 0.27053)

Relative Risk
Parameter Estimate: 1.277
p-value: 3.7694e-07
95% Conf Interval: (1.1621, 1.4034)

log(RR): 0.24454
variance(log(RR)): 0.002317

Odds Ratio
Parameter Estimate: 2.5477
p-value: 0.00025334
95% Conf Interval: (1.5438, 4.2045)

log(OR): 0.93518
variance(log(OR)): 0.065329

```

Let us take a closer look at the results. In the beginning are reported the fractions by which the separate algorithms contribute to the combined algorithm. After that are given estimates of the causal contrasts together with their estimated variances and 95 % confidence intervals. The variance of each contrast (on log-scale for RR and OR) is estimated as the variance of the empirical influence curve divided by n , the number of i.i.d. units of observation. Furthermore, causal risk differences are estimated also for those factually exposed and unexposed, respectively.

Note that because this analysis was based on sample data, the estimates are most probably deviating from the true values because of pure random error. Therefore it is not possible to assess the magnitude of a possible bias from a single sample.

4. **Homework.** When you have more time, try to run `tmle` on as large sample as is possible and compare its results with previous ones computed for the whole target population.

2.16 Nested case-control study and case-cohort study: Risk factors of coronary heart disease

In this exercise we shall apply both the nested case-control (NCC) design and the case-cohort (CC) design in sampling control subjects from a defined cohort or closed study population. The case group comprises those cohort members who die from coronary heart disease (CHD) during a > 20 years follow-up of the cohort. The risk factors of interest are cigarette smoking, systolic blood pressure, and total cholesterol level.

Our study population is an occupational cohort comprising 1501 men working in blue-collar jobs in one Nordic country. Eligible subjects had no history of coronary heart disease when recruited to the study in the early 1990s. Smoking habits and many other items were inquired at baseline by a questionnaire, and blood pressure was measured by a research nurse, the values being written down on the questionnaire. Serum samples were also taken from the cohort members at the same time and were stored in a freezer. For some reason, the data in the questionnaires were not entered to any computer file, but the questionnaires were kept in a safe storehouse for further purposes. Also, no biochemical analyses were initially performed for the sera collected from the participants. However, dates of birth and dates of entry to the study were recorded in an electronic file.

In 2010 the study was suddenly reactivated by those investigators of the original team who were still alive then. As the first step mortality follow-up of the cohort members was executed by record linkage to the national population register, from which the dates of death and emigration were obtained. Another linkage was performed with the national register of causes of death in order to get the deaths from coronary heart disease identified. As a result a data file `occoh.txt` was completed containing the following variables:

<code>id</code>	= identification number,
<code>birth</code>	= date of birth,
<code>entry</code>	= date of recruitment and baseline measurements,
<code>exit</code>	= date of exit from mortality follow-up,
<code>death</code>	= indicator for vital status at the end of follow-up, = 1, if dead from any cause, and = 0, if alive,
<code>chdeath</code>	= indicator for death from coronary heart disease, = 1, if “yes”, and 0, if “no”.

This exercise is divided into five main parts:

- (1) Description of the study base or the follow-up experience of the whole cohort, identification of the cases and illustrating the risk sets.
- (2) Nested case-control study within the cohort: (i) selection of controls by risk set or time-matched sampling using function `ccwc()` in package `Epi`, (ii) collection of exposure data for cases and controls from the pertinent data base of the whole cohort to the case-control data set using function `merge()`, and (iii) analysis of the case-control data set with stratified Cox model using function `clogit()` in package `survival()`,
- (3) Case-cohort study within the cohort: (i) selection of a subcohort by simple random sampling from the cohort, (ii) collection of exposure data for subcohort members and cases, and (iii) analysis of the case-cohort data set with Cox model by weighted partial

likelihood including appropriate weighting and correction of estimated covariance matrix for the model coefficients using function `cch()` in package `survival()`.

- (4) Comparison of results from all previous analyses, also with those from a full cohort design.
- (5) Further tasks and homework.

2.16.1 Reading the cohort data, illustrating the study base and risk sets

5. Load the packages `Epi` and `survival`. Read in the cohort data file and name the resulting data frame as `oc`. See its structure and print the univariate summaries.

```
> library(Epi)
> library(survival)
> url <- "https://raw.githubusercontent.com/SPE-R/SPE/master/pracs/data"
> oc <- read.table( paste(url, "occoh.txt", sep = "/"), header=TRUE)
> str(oc)

'data.frame':      1501 obs. of  6 variables:
 $ id      : int   1 2 3 4 5 6 7 8 9 10 ...
 $ birth   : chr   "1943-02-19" "1934-07-06" "1939-03-05" "1939-07-03" ...
 $ entry   : chr   "1990-08-14" "1990-08-14" "1990-08-14" "1990-08-14" ...
 $ exit    : chr   "2009-12-31" "2009-12-31" "2009-12-31" "2009-12-31" ...
 $ death   : int   0 0 0 0 1 1 1 1 0 0 ...
 $ chdeath : int   0 0 0 0 0 0 0 1 0 0 ...

> summary(oc)

      id      birth      entry      exit
Min.   :    1  Length:1501  Length:1501  Length:1501
1st Qu.: 376  Class :character  Class :character  Class :character
Median : 751  Mode  :character  Mode  :character  Mode  :character
Mean    : 751
3rd Qu.:1126
Max.    :1501

      death      chdeath
Min.   :0.0000  Min.   :0.00000
1st Qu.:0.0000  1st Qu.:0.00000
Median :0.0000  Median :0.00000
Mean    :0.1972  Mean    :0.07995
3rd Qu.:0.0000  3rd Qu.:0.00000
Max.    :1.0000  Max.    :1.00000
```

6. It is convenient to change all the dates into fractional calendar years

```
> oc$ybirth <- cal.yr(oc$birth)
> oc$yentry <- cal.yr(oc$entry)
> oc$yexit  <- cal.yr(oc$exit)
```

We shall also compute the age at entry and at exit, respectively, as age will be the main time scale in our analyses.

```
> oc$agentry <- oc$yentry - oc$ybirth
> oc$agexit <- oc$yexit - oc$ybirth
```

7. As the next step we shall create a `lexis` object from the data frame along the calendar period and age axes, and as the outcome event we specify the coronary death.

```
> oc.lex <- Lexis( entry = list( per = yentry,
+                               age = yentry - ybirth ),
+                 exit = list( per = yexit),
+                 exit.status = chdeath,
+                 id = id, data = oc)
```

NOTE: `entry.status` has been set to 0 for all.

```
> str(oc.lex)
```

```
Classes 'Lexis' and 'data.frame':      1501 obs. of  17 variables:
 $ per      : 'cal.yr' num  1991 1991 1991 1991 1991 ...
 $ age      : 'cal.yr' num  47.5 56.1 51.4 51.1 55.5 ...
 $ lex.dur  : 'cal.yr' num  19.4 19.4 19.4 19.4 15.6 ...
 $ lex.Cst  : num  0 0 0 0 0 0 0 0 0 0 ...
 $ lex.Xst  : int  0 0 0 0 0 0 0 1 0 0 ...
 $ lex.id   : int  1 2 3 4 5 6 7 8 9 10 ...
 $ id       : int  1 2 3 4 5 6 7 8 9 10 ...
 $ birth    : chr   "1943-02-19" "1934-07-06" "1939-03-05" "1939-07-03" ...
 $ entry    : chr   "1990-08-14" "1990-08-14" "1990-08-14" "1990-08-14" ...
 $ exit     : chr   "2009-12-31" "2009-12-31" "2009-12-31" "2009-12-31" ...
 $ death    : int  0 0 0 0 1 1 1 1 0 0 ...
 $ chdeath  : int  0 0 0 0 0 0 0 1 0 0 ...
 $ ybirth   : 'cal.yr' num  1943 1935 1939 1940 1935 ...
 $ yentry   : 'cal.yr' num  1991 1991 1991 1991 1991 ...
 $ yexit    : 'cal.yr' num  2010 2010 2010 2010 2006 ...
 $ agentry  : 'cal.yr' num  47.5 56.1 51.4 51.1 55.5 ...
 $ agexit   : 'cal.yr' num  66.9 75.5 70.8 70.5 71.1 ...
 - attr(*, "time.scales")= chr [1:2] "per" "age"
 - attr(*, "time.since")= chr [1:2] "" ""
 - attr(*, "breaks")=List of 2
 ..$ per: NULL
 ..$ age: NULL
```

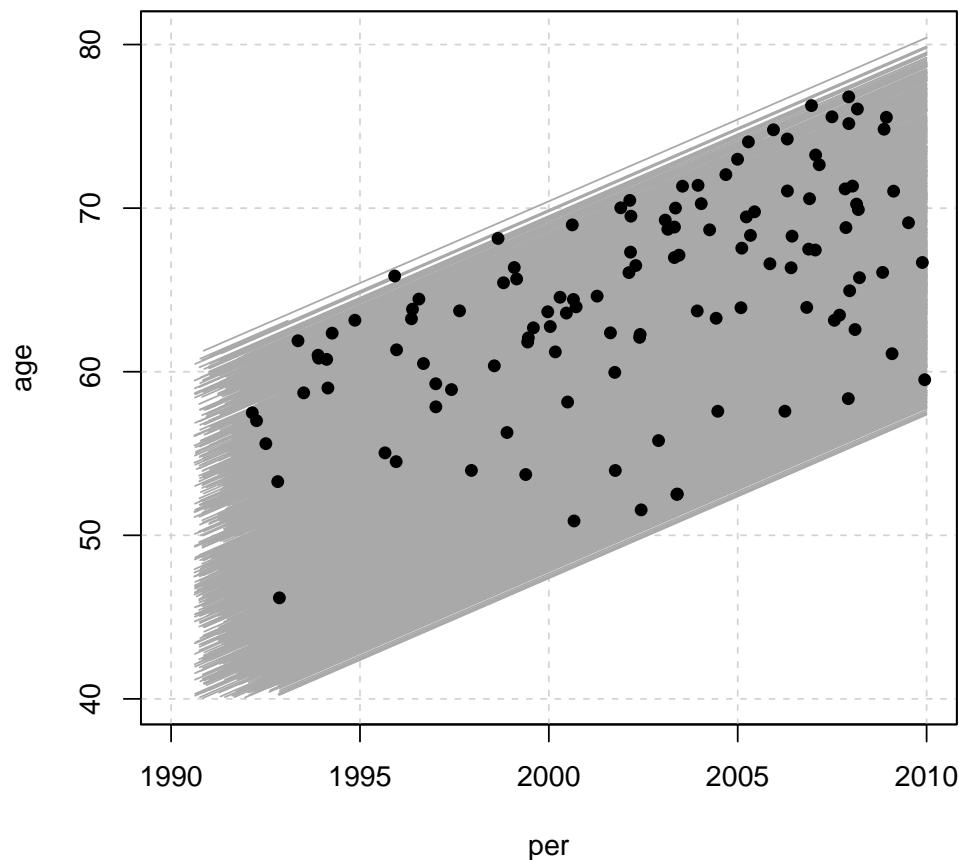
```
> summary(oc.lex)
```

Transitions:

	From	To	Records:	Events:	Risk time:	Persons:
	0	1	1501	120	25280.91	1501

8. At this stage it is informative to examine a graphical presentation of the follow-up lines and outcome cases in a conventional Lexis diagram. Make use of the `plot` method for `Lexis` objects. Gray lifelines are drawn and a bullet is put at the exit point of those lifelines that end with the outcome event.

```
> par(mfrow=c(1,1))
> plot( oc.lex, xlim=c(1990, 2010),grid=TRUE )
> points( oc.lex, pch=c(NA, 16)[oc.lex$lex.Xst+1] )
```

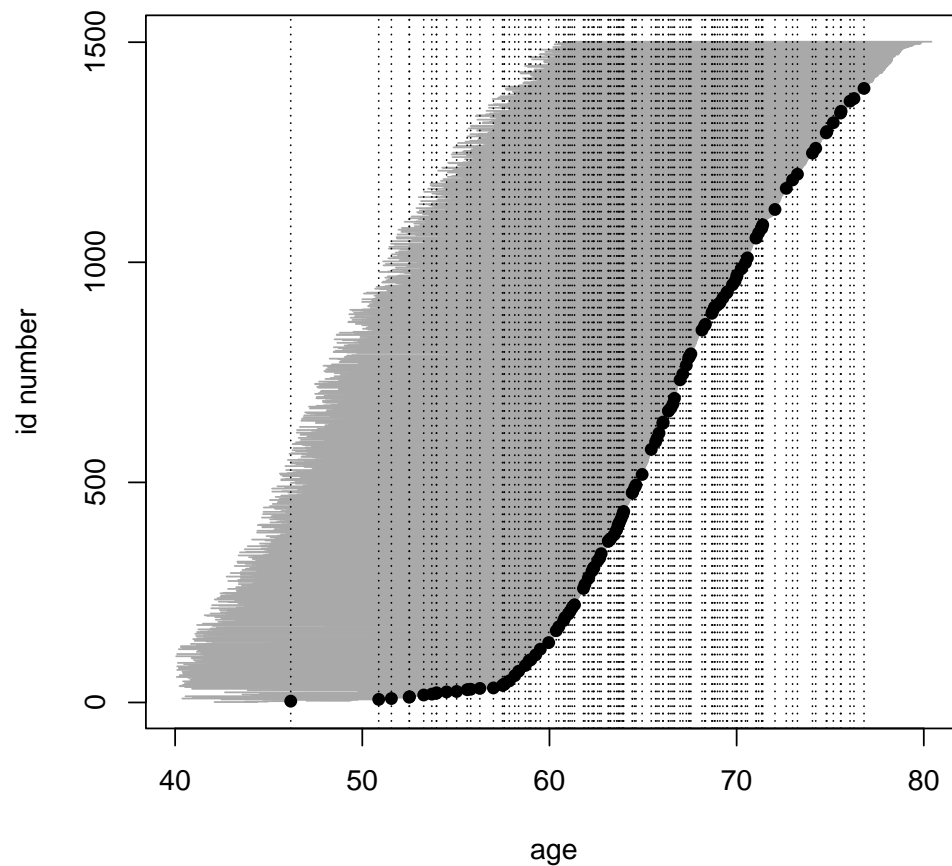



9. As age is here the main time axis, we shall graphically illustrate the **study base**, *i.e.* the follow-up lines and outcome events, only along the age scale, being ordered by age at exit. Vertical lines at those ages when new coronary deaths occur are drawn to identify the pertinent **risk sets**. For that purpose it is useful first to sort the data frame and the **Lexis** object jointly by age at exit & age at entry, and to give a new ID number according to that order.

```
> oc.ord <- cbind(ID = 1:1501, oc[ order( oc$agexit, oc$agentry), ] )
> oc.lexord <- Lexis( entry = list( age = agentry ),
+                   exit = list( age = agexit),
+                   exit.status = chdeath,
+                   id = ID, data = oc.ord)
```

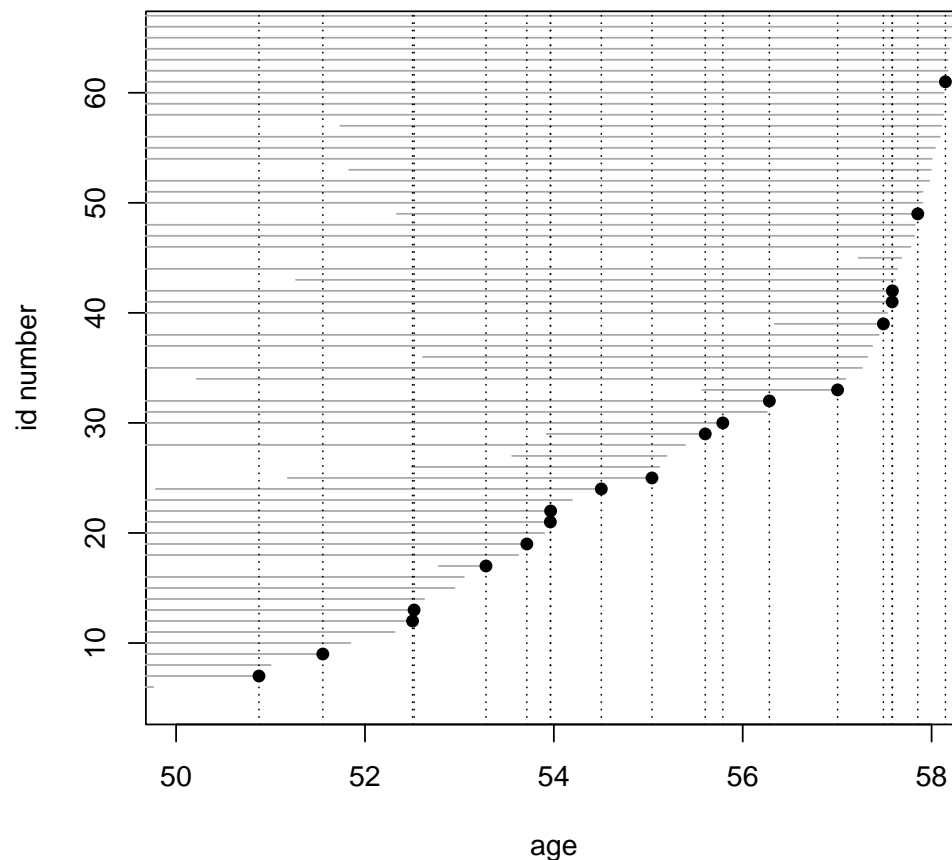
NOTE: entry.status has been set to 0 for all.

```
> plot(oc.lexord, "age")
> points(oc.lexord, pch=ifelse(oc.lexord$lex.Xst==1, 16, NA) )
> with( subset(oc.lexord, lex.Xst==1),
+       abline( v=agexit, lty=3))
```



10. For a closer look, we now zoom the graphical illustration of the risk sets into event times occurring between 50 to 58 years. – Copy the last four lines from the previous item and add arguments `xlim` and `ylim` to the call of `plot()`.

```
> plot(oc.lexord, "age", xlim=c(50, 58), ylim=c(5, 65))
> points(oc.lexord, "age", pch=ifelse(oc.lexord$lex.Xst==1, 16, NA))
> with( subset(oc.lexord, lex.Xst==1),
+       abline( v=agexit, lty=3))
```



2.16.2 Nested case-control study

We shall now employ the strategy of **risk-set sampling** or **time-matched** sampling of controls, *i.e.* we are conducting a **nested case-control study** within the cohort.

11. The risk sets are defined according to the age at diagnosis of the case. Further matching is applied for age at entry by 1-year agebands. For this purpose we first generate a categorical variable **agen2** for age at entry

```
> oc.lex$agen2 <- cut(oc.lex$agentry, br = seq(40, 62, 1) )
```

Matched sampling from risk sets may be carried out using function `ccwc()` found in the `Epi` package. Its main arguments are the times of **entry** and **exit** which specify the time at risk along the main time scale (here age), and the outcome variable to be given in the **fail** argument. The number of controls per case is set to be two, and the additional matching factor is given. – After setting the RNG seed (with your own number), make a call of this function and see the structure of the resulting data frame `cactrl` containing the cases and the chosen individual controls.

```
> set.seed(98623)
> cactrl <-
+   ccwc(entry=agency, exit=agexit, fail=chdeath,
+       controls = 2, match= agen2,
+       include = list(id, agency),
+       data=oc.lex, silent=FALSE)
```

Sampling risk sets:

```
> str(cactrl)
```

```
'data.frame':      360 obs. of  7 variables:
 $ Set      : num  1 1 1 2 2 2 3 3 3 4 ...
 $ Map      : num  8 1423 1 95 381 ...
 $ Time     : num  63.9 63.9 63.9 66.7 66.7 ...
 $ Fail     : num  1 0 0 1 0 0 1 0 0 1 ...
 $ agen2    : Factor w/ 22 levels "(40,41]","(41,42]","...: 8 8 8 8 8 8 8 8 8 ...
 $ id       : int   8 1423 1 95 381 106 115 44 1343 504 ...
 $ agency   : num  47.7 47.9 47.5 47.5 48 ...
```

Check the meaning of the four first columns of the case-control data frame from the help page of function `ccwc()`.

12. Now we shall start collecting data on the risk factors for the cases and their matched controls, including determination of the total cholesterol levels from the frozen sera! The storehouse of the risk factor measurements for the whole cohort is file `occoh-Xdata.txt`. It contains values of the following variables.

```
id =   identification number, the same as in occoh.txt,
smok = cigarette smoking with categories,
       1: "never", 2: "former", 3: "1-14/d", 4: "15+/d",
sbp  = systolic blood pressure (mmHg),
tchol = total cholesterol level (mmol/l).
```

```
> ocX <- read.table( paste(url, "occoh-Xdata.txt", sep = "/"), header=TRUE)
> str(ocX)
```

```
'data.frame':      1501 obs. of  6 variables:
 $ id      : int   1 2 3 4 5 6 7 8 9 10 ...
 $ birth   : chr   "1943-02-19" "1934-07-06" "1939-03-05" "1939-07-03" ...
 $ entry   : chr   "1990-08-14" "1990-08-14" "1990-08-14" "1990-08-14" ...
 $ smok    : int   4 3 3 1 2 2 1 2 1 1 ...
 $ sbp     : int  130 128 157 102 138 119 155 154 164 124 ...
 $ tchol   : num   7.56 6.55 8.13 5.93 7.92 5.9 7.28 7.43 5.34 6.24 ...
```

13. In the next step we collect the values of the risk factors for our cases and controls by merging the case-control data frame and the storehouse file. In this operation we utilize function `merge()` to select columns of two data frames: `cactrl` (all columns) and `ocX` (four columns) and to merge these into a single file (see exercise 1.1, subsection 1.1.8, where `merge()` was introduced). The `id` variable in both files is used as the key to link each individual case or control with his own data on risk factors.

```
> oc.ncc <- merge(cactrl, ocX[, c("id", "smok", "tchol", "sbp")],
+   by = "id")
> str(oc.ncc)

'data.frame':      360 obs. of  10 variables:
 $ id      : int  1 8 10 12 14 28 37 41 41 42 ...
 $ Set     : num  1 1 77 9 44 50 5 5 7 9 ...
 $ Map     : num  1 8 10 12 14 28 37 41 41 42 ...
 $ Time    : num  63.9 63.9 73 70.3 75.2 ...
 $ Fail    : num  0 1 0 0 0 0 0 1 0 1 ...
 $ agen2   : Factor w/ 22 levels "(40,41]","(41,42]",...: 8 8 20 17 19 19 1 1 1 17 ...
 $ agentry : num  47.5 47.7 59.5 56.1 58.7 ...
 $ smok    : int  4 2 1 2 4 1 3 4 4 2 ...
 $ tchol   : num  7.56 7.43 6.24 5 3.73 4.56 5.15 6.09 6.09 5.41 ...
 $ sbp     : int  130 154 124 148 165 230 116 125 125 156 ...
```

14. We shall treat smoking as categorical and total cholesterol and systolic blood pressure as quantitative risk factors, but the values of the latter will be divided by 10 to get more interpretable effect estimates.

Convert the smoking variable into a factor.

```
> oc.ncc$smok <- factor(oc.ncc$smok,
+   labels = c("never", "ex", "1-14/d", ">14/d"))
```

15. It is useful to start the analysis of case-control data by simple tabulations by the categorized risk factors. Crude estimates of the rate ratios associated with them, in which matching is ignored, can be obtained as follows. We shall focus on smoking

```
> stat.table( index = list( smok, Fail ),
+   contents = list( count(), percent(smok) ),
+   margins = T, data = oc.ncc )
```

```
-----
      -----Fail-----
smok      0      1  Total
-----
never      85      31    116
          35.4    25.8    32.2

ex          61      19     80
          25.4    15.8    22.2

1-14/d      54      42     96
          22.5    35.0    26.7

>14/d       40      28     68
          16.7    23.3    18.9

Total      240     120    360
          100.0   100.0   100.0
-----
```

```
> smok.crncc <- glm( Fail ~ smok, family=binomial, data = oc.ncc)
> round(ci.exp(smok.crncc), 3)
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.365	0.242	0.550
smokex	0.854	0.442	1.651
smok1-14/d	2.133	1.199	3.794
smok>14/d	1.919	1.018	3.619

16. A proper analysis takes into account matching that was employed in the selection of controls for each case from the pertinent risk set, further restricted to subjects who were about the same age at entry as the case was. Also, adjustment for the other risk factors is desirable. In this analysis function `clogit()` in `survival` package is utilized. It is in fact a wrapper of function `coxph()`.

```
> m.clogit <- clogit( Fail ~ smok + I(sbp/10) + tchol +
+ strata(Set), data = oc.ncc )
> summary(m.clogit)
```

Call:

```
coxph(formula = Surv(rep(1, 360L), Fail) ~ smok + I(sbp/10) +
      tchol + strata(Set), data = oc.ncc, method = "exact")
```

```
n= 360, number of events= 120
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
smokex	-0.22100	0.80172	0.35085	-0.630	0.52877
smok1-14/d	0.59186	1.80734	0.29894	1.980	0.04772 *
smok>14/d	0.56616	1.76149	0.33326	1.699	0.08935 .
I(sbp/10)	0.11171	1.11818	0.05453	2.049	0.04050 *
tchol	0.40091	1.49319	0.11142	3.598	0.00032 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
smokex	0.8017	1.2473	0.4031	1.595
smok1-14/d	1.8073	0.5533	1.0060	3.247
smok>14/d	1.7615	0.5677	0.9167	3.385
I(sbp/10)	1.1182	0.8943	1.0048	1.244
tchol	1.4932	0.6697	1.2003	1.858

Concordance= 0.679 (se = 0.046)

Likelihood ratio test= 28.81 on 5 df, p=3e-05

Wald test = 24.31 on 5 df, p=2e-04

Score (logrank) test = 27.31 on 5 df, p=5e-05

```
> round(ci.exp(m.clogit), 3)
```

	exp(Est.)	2.5%	97.5%
smokex	0.802	0.403	1.595
smok1-14/d	1.807	1.006	3.247
smok>14/d	1.761	0.917	3.385
I(sbp/10)	1.118	1.005	1.244
tchol	1.493	1.200	1.858

Compare these with the crude estimates obtained above.

2.16.3 Case-cohort study

Now we start applying the second major outcome-selective sampling strategy for collecting exposure data from a big study population

17. The subcohort is selected as a simple random sample ($n = 260$) from the whole cohort. The id-numbers of the individuals that are selected will be stored in vector `subcids`, and `subcind` is an indicator for inclusion to the subcohort.

```
> N <- 1501; n <- 260
> set.seed(15792)
> subcids <- sample(N, n)
> oc.lexord$subcind <- 1*(oc.lexord$id %in% subcids)
```

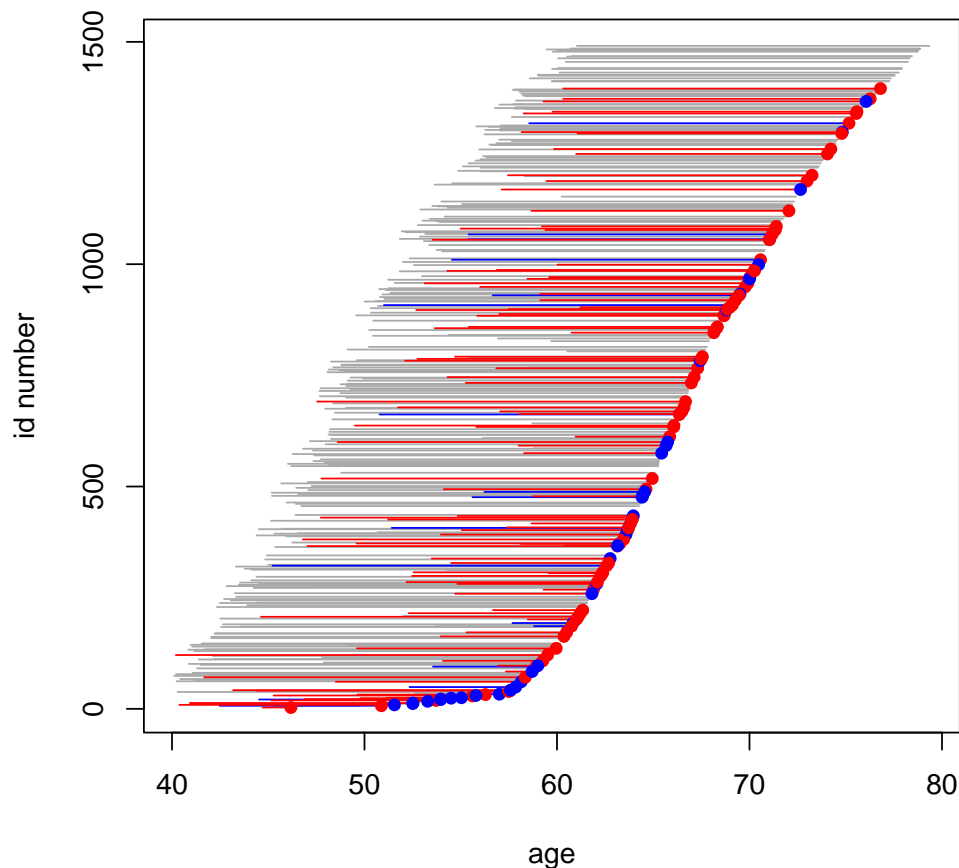
18. We form the data frame `oc.cc` to be used in the subsequent analysis selecting the union of the subcohort members and the case group from the data frame of the full cohort. After that we collect the data of the risk factors from the data storehouse for the subjects in the case-cohort data

```
> oc.cc <- subset( oc.lexord, subcind==1 | chdeath ==1)
> oc.cc <- merge( oc.cc, ocX[, c("id", "smok", "tchol", "sbp")],
+   by = "id")
> str(oc.cc)

Classes 'Lexis' and 'data.frame':    362 obs. of  21 variables:
 $ id      : int  8 10 34 40 41 42 43 45 51 62 ...
 $ age     : num  47.7 59.5 51.9 45.2 40.2 ...
 $ lex.dur : num  16.21 19.38 19.36 4.59 19.32 ...
 $ lex.Cst : num  0 0 0 0 0 0 0 0 0 0 ...
 $ lex.Xst : int  1 0 0 0 1 1 1 0 1 1 ...
 $ lex.id  : int  430 1483 1074 6 121 987 746 486 1056 663 ...
 $ ID      : int  430 1483 1074 6 121 987 746 486 1056 663 ...
 $ birth   : chr  "1942-11-24" "1931-03-01" "1938-09-14" "1945-06-22" ...
 $ entry   : chr  "1990-08-15" "1990-08-15" "1990-08-20" "1990-08-21" ...
 $ exit    : chr  "2006-10-30" "2009-12-31" "2009-12-31" "1995-03-26" ...
 $ death   : int  1 0 0 1 1 1 1 0 1 1 ...
 $ chdeath : int  1 0 0 0 1 1 1 0 1 1 ...
 $ ybirth  : num  1943 1931 1939 1945 1950 ...
 $ yentry  : num  1991 1991 1991 1991 1991 ...
 $ yexit   : num  2007 2010 2010 1995 2010 ...
 $ agency  : num  47.7 59.5 51.9 45.2 40.2 ...
 $ agexit  : num  63.9 78.8 71.3 49.8 59.5 ...
 $ subcind : num  0 1 1 1 0 0 0 1 1 0 ...
 $ smok    : int  2 1 1 4 4 2 3 2 1 2 ...
 $ tchol   : num  7.43 6.24 5.8 5.88 6.09 5.41 5.72 5.98 7.12 5.57 ...
 $ sbp     : int  154 124 113 141 125 156 128 115 137 173 ...
 - attr(*, "breaks")=List of 1
 ..$ age: NULL
 - attr(*, "time.scales")= chr "age"
 - attr(*, "time.since")= chr ""
```

19. We shall now create a graphical illustration of the lifelines contained in the case-cohort data. Lines for the subcohort non-cases are grey without bullet at exit, those for subcohort cases are blue with blue bullet at exit, and for cases outside the subcohort the lines are red and dotted with red bullets at exit.

```
> plot( subset(oc.cc, chdeath==0), "age")
> lines( subset(oc.cc, chdeath==1 & subcind==1), col="blue")
> lines( subset(oc.cc, chdeath==1 & subcind==0), col="red")
> points(subset(oc.cc, chdeath==1), pch=16,
+        col=c("blue", "red")[oc.cc$subcind+1])
```



20. Define the categorical smoking variable again.

```
> oc.cc$smok <- factor(oc.cc$smok,
+ labels = c("never", "ex", "1-14/d", ">14/d"))
```

A crude estimate of the hazard ratio for the various smoking categories k vs. non-smokers ($k = 1$) can be obtained by tabulating cases (D_k) and person-years (y_k) in the subcohort by smoking and then computing the relevant exposure odds ratio for each category:

$$\text{HR}_k^{\text{crude}} = \frac{D_k/D_1}{y_k/y_1}$$

```
> sm.cc <- stat.table( index = smok,
+ contents = list( Cases = sum(lex.Xst), Pyrs = sum(lex.dur) ),
+ margins = T, data = oc.cc)
> print(sm.cc, digits = c(sum=0, ratio=1))
```



```

-----
smok      Cases    Pyrs
-----
never      31      2071
ex         19      1174
1-14/d     42      1399
>14/d      28      846

Total      120      5489
-----

> HRcc <- (sm.cc[ 1, -5]/sm.cc[ 1, 1])/(sm.cc[ 2, -5]/sm.cc[2, 1])
> round(HRcc, 3)

never      ex 1-14/d  >14/d
1.000    1.081    2.006    2.211

```

Do these estimates resemble those obtained from nested case-control data?

21. To estimate the rate ratios associated with smoking and adjusted for the other risk factors we now fit the pertinent Cox model applying the method of *weighted partial likelihood* as presented by Ling & Ying (1993) and Barlow (1994). This analysis can be done using function `cch()` in package `survival` with `method = "LinYing"`

```

> oc.cc$survobj <- with(oc.cc, Surv(agency, agexit, chdeath) )
> cch.LY <- cch( survobj ~  smok + I(sbp/10) + tchol, stratum=NULL,
+   subcoh = ~subcind, id = ~id, cohort.size = N, data = oc.cc,
+   method = "LinYing" )
> summary(cch.LY)

Case-cohort analysis,x$method, LinYing
with subcohort of 260 from cohort of 1501

Call: cch(formula = survobj ~ smok + I(sbp/10) + tchol, data = oc.cc,
  subcoh = ~subcind, id = ~id, stratum = NULL, cohort.size = N,
  method = "LinYing")

Coefficients:
              Coef      HR (95%  CI)      p
smokex       -0.096  0.909  0.457  1.806  0.785
smok1-14/d    0.769  2.157  1.180  3.943  0.012
smok>14/d     1.085  2.959  1.532  5.718  0.001
I(sbp/10)     0.218  1.244  1.119  1.383  0.000
tchol         0.350  1.419  1.152  1.748  0.001

```

2.16.4 Full cohort analysis and comparisons

Finally, suppose the investigators after all could afford to collect the data on risk factors from the storehouse for the whole cohort.

22. Let us form the data frame corresponding to the full cohort design and convert again smoking to be categorical.

```
> oc.full <- merge( oc.lex, ocX[, c("id", "smok", "tchol", "sbp")],
+   by.x = "id", by.y = "id")
> oc.full$smok <- factor(oc.full$smok,
+   labels = c("never", "ex", "1-14/d", ">14/d"))
```

Juts for comparison with the corresponding analysis in case-cohort data perform a similar crude estimation of hazard ratios associated with smoking.

```
> sm.coh <- stat.table( index = smok,
+   contents = list( Cases = sum(lex.Xst), Pyrs = sum(lex.dur) ),
+   margins = T, data = oc.full)
> print(sm.coh, digits = c(sum=0, ratio=1))
```

smok	Cases	Pyrs
never	31	10363
ex	19	4879
1-14/d	42	6246
>14/d	28	3793
Total	120	25281

```
> HRcoh <- (sm.coh[ 1, -5]/sm.coh[ 1, 1])/(sm.coh[ 2, -5]/sm.coh[2, 1])
> round(HRcoh, 3)
```

never	ex	1-14/d	>14/d
1.000	1.302	2.248	2.468

23. Fit now the ordinary Cox model to the full cohort. There is no need to employ extra tricks upon the ordinary `coxph()` fit.

```
> cox.coh <- coxph( Surv(agentry, agexit, chdeath) ~
+   smok + I(sbp/10) + tchol, data = oc.full)
> summary(cox.coh)
```

Call:
coxph(formula = Surv(agentry, agexit, chdeath) ~ smok + I(sbp/10) +
tchol, data = oc.full)

n= 1501, number of events= 120

	coef	exp(coef)	se(coef)	z	Pr(> z)
smokex	0.10955	1.11577	0.29240	0.375	0.707922
smok1-14/d	0.72567	2.06612	0.23704	3.061	0.002203 **
smok>14/d	0.95054	2.58711	0.26198	3.628	0.000285 ***
I(sbp/10)	0.14372	1.15456	0.04096	3.509	0.000450 ***
tchol	0.26517	1.30366	0.07089	3.740	0.000184 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
smokex	1.116	0.8962	0.629	1.979
smok1-14/d	2.066	0.4840	1.298	3.288
smok>14/d	2.587	0.3865	1.548	4.323
I(sbp/10)	1.155	0.8661	1.065	1.251

```
tchol      1.304      0.7671      1.135      1.498
```

```
Concordance= 0.681 (se = 0.026 )
```

```
Likelihood ratio test= 41.16 on 5 df, p=9e-08
```

```
Wald test          = 42.05 on 5 df, p=6e-08
```

```
Score (logrank) test = 43.29 on 5 df, p=3e-08
```

24. Lastly, a comparison of the point estimates and standard errors between the different designs, including variants of analysis for the case-cohort design, can be performed.

```
> betas <- cbind( coef(cox.coh), coef(m.clogit), coef(cch.LY) )
> colnames(betas) <- c("coh", "ncc", "cch.LY")
> round(betas, 3)
```

```
      coh      ncc cch.LY
smokex    0.110 -0.221 -0.096
smok1-14/d 0.726  0.592  0.769
smok>14/d  0.951  0.566  1.085
I(sbp/10)  0.144  0.112  0.218
tchol      0.265  0.401  0.350
```

```
> SEs <- cbind( sqrt( diag( cox.coh$var ) ),
+              sqrt( diag( m.clogit$var ) ),
+              sqrt( diag( cch.LY$var ) ) )
> colnames(SEs) <- colnames(betas)
> round(SEs, 3)
```

```
      coh      ncc cch.LY
smokex    0.292 0.351 0.350
smok1-14/d 0.237 0.299 0.308
smok>14/d  0.262 0.333 0.336
I(sbp/10)  0.041 0.055 0.054
tchol      0.071 0.111 0.106
```

You will notice that the point estimates of the coefficients obtained from the full cohort, nested case-control, and case-cohort analyses, respectively, are somewhat variable.

However, the standard errors from the NCC and CC analyses should be quite similar when the numbers of cases and non-cases are similar.

2.16.5 Further exercises and homework

25. If you have time, you could run both the NCC study and CC study again but now with a larger control group or subcohort; for example 4 controls per case in NCC and $n = 520$ as the subcohort size in CC. Remember resetting the seed first. Pay attention in the results to how much closer will be the point estimates and the proper SEs to those obtained from the full cohort design.
26. Instead of simple linear terms for `sbp` and `tchol` you could try to fit spline models to describe their effects.
27. A popular alternative to weighted partial likelihood in the analysis of case-cohort data is the *pseudo-likelihood method* (Prentice 1986), which is based on “late entry” to follow-up of the case subjects not belonging to the subcohort. The way to do this is provided by

- function `cch()` which you can apply directly to the case-cohort data `oc.cc` as before but now with `method = "Prentice"`. – Try this and compare the results with those obtained by weighted partial likelihood in model `cch.LY`.
28. Yet another computational solution for maximizing weighted partial likelihood is provided by a combination of functions `twophase()` and `svycoxph()` of the `survey` package. The approach is illustrated with an example in a vignette “Two-phase designs in epidemiology” by Thomas Lumley (see <http://cran.r-project.org/web/packages/survey/vignettes/epi.pdf>). – You can try this at home and check that you would obtain similar results as with model `cch.LY`.

2.17 Time-dependent variables and multiple states

2.17.1 The renal failure dataset

1. The dataset is in Stata-format, so we read the dataset using `read.dta` from the `foreign` package (which is part of the standard R-distribution):

```
library( Epi )
library( foreign )
clear()
renal <- read.dta(
  "https://raw.githubusercontent.com/SPE-R/SPE/master/pracs/data/renal.dta" )
# renal <- read.dta( "http://BendixCarstensen.com/SPE/data/renal.dta" )
# renal <- read.dta( "../data/renal.dta" )
renal$sex <- factor( renal$sex, labels=c("M","F") )
head(renal)
```

	id	sex	dob	doe	dor	dox	event
1	17	M	1967.944	1996.013	NA	1997.094	2
2	26	F	1959.306	1989.535	1989.814	1996.136	1
3	27	F	1962.014	1987.846	NA	1993.239	3
4	33	M	1950.747	1995.243	1995.717	2003.993	0
5	42	F	1961.296	1987.884	1996.650	2003.955	0
6	46	F	1952.374	1983.419	NA	1991.484	2

2. We use the `Lexis` function to declare the data as survival data with age, calendar time and time since entry into the study as timescales. Note that any coding of event > 0 will be labeled “ESRD”, i.e. renal death (death of kidney (transplant or dialysis), or person).

Note that you must make sure that the “alive” state (here `NRA`) is the first, as `Lexis` assumes that everyone starts in this state (unless of course `entry.status` is specified):

```
Lr <- Lexis( entry = list( per = doe,
                          age = doe-dob,
                          tfi = 0 ),
            exit = list( per = dox ),
            exit.status = factor( event>0, labels=c("NRA","ESRD") ),
            data = renal )
```

NOTE: `entry.status` has been set to `"NRA"` for all.

```
str( Lr )
```

```
Classes 'Lexis' and 'data.frame':      125 obs. of  14 variables:
 $ per      : num  1996 1990 1988 1995 1988 ...
 $ age      : num  28.1 30.2 25.8 44.5 26.6 ...
 $ tfi      : num  0 0 0 0 0 0 0 0 0 0 ...
 $ lex.dur  : num  1.08 6.6 5.39 8.75 16.07 ...
 $ lex.Cst  : Factor w/ 2 levels "NRA","ESRD": 1 1 1 1 1 1 1 1 1 1 ...
 $ lex.Xst  : Factor w/ 2 levels "NRA","ESRD": 2 2 2 1 1 2 2 1 2 1 ...
 $ lex.id   : int   1 2 3 4 5 6 7 8 9 10 ...
 $ id       : num   17 26 27 33 42 46 47 55 62 64 ...
 $ sex      : Factor w/ 2 levels "M","F": 1 2 2 1 2 2 1 1 2 1 ...
 $ dob      : num   1968 1959 1962 1951 1961 ...
 $ doe      : num   1996 1990 1988 1995 1988 ...
 $ dor      : num   NA 1990 NA 1996 1997 ...
 $ dox      : num   1997 1996 1993 2004 2004 ...
```

```

$ event : num 2 1 3 0 0 2 1 0 2 0 ...
- attr(*, "time.scales")= chr [1:3] "per" "age" "tfi"
- attr(*, "time.since")= chr [1:3] "" "" ""
- attr(*, "breaks")=List of 3
..$ per: NULL
..$ age: NULL
..$ tfi: NULL

summary( Lr )

```

Transitions:

```

To
From  NRA  ESRD  Records:  Events: Risk time:  Persons:
    NRA  48   77      125      77   1084.67      125

```

3. We can visualize the follow-up in a Lexis-diagram, using the `plot` method for Lexis objects.

```

plot( Lr, col="black", lwd=3 )
subset( Lr, age<0 )

lex.id    per    age tfi lex.dur lex.Cst lex.Xst  id sex    dob    doe dor    dox
   88 1989.34 -38.81  0    3.5    NRA    ESRD 586  M 2028.155 1989.343 NA 1992.839
event
1

```

The result is the left hand plot in figure 2.8, and we see a person entering at a negative age, clearly because he is born way out in the future.

4. So we correct the data and make the correct plot, as seen in the right hand plot in figure 2.8:

```

Lr <- transform( Lr, dob = ifelse( dob>2000, dob-100, dob ),
                  age = ifelse( dob>2000, age+100, age ) )
subset( Lr, id==586 )

lex.id    per    age tfi lex.dur lex.Cst lex.Xst  id sex    dob    doe dor    dox
   88 1989.34  61.19  0    3.5    NRA    ESRD 586  M 1928.155 1989.343 NA 1992.839
event
1

plot( Lr, col="black", lwd=3 )

```

5. We can produce a slightly more fancy Lexis diagram. Note that we have a x -axis of 40 years, and a y -axis of 80 years, so when specifying the output file adjust the *total* width of the plot so that the use `mai mai` to specify the margins of the plot leaves a plotting area twice as high as wide. The `mai` argument to `par` gives the margins in inches, so the total size of the horizontal and vertical margins is 1 inch, to which we add $80/5$ in the height, and $40/5$ in the horizontal direction, each giving exactly 5 years per inch in physical size.

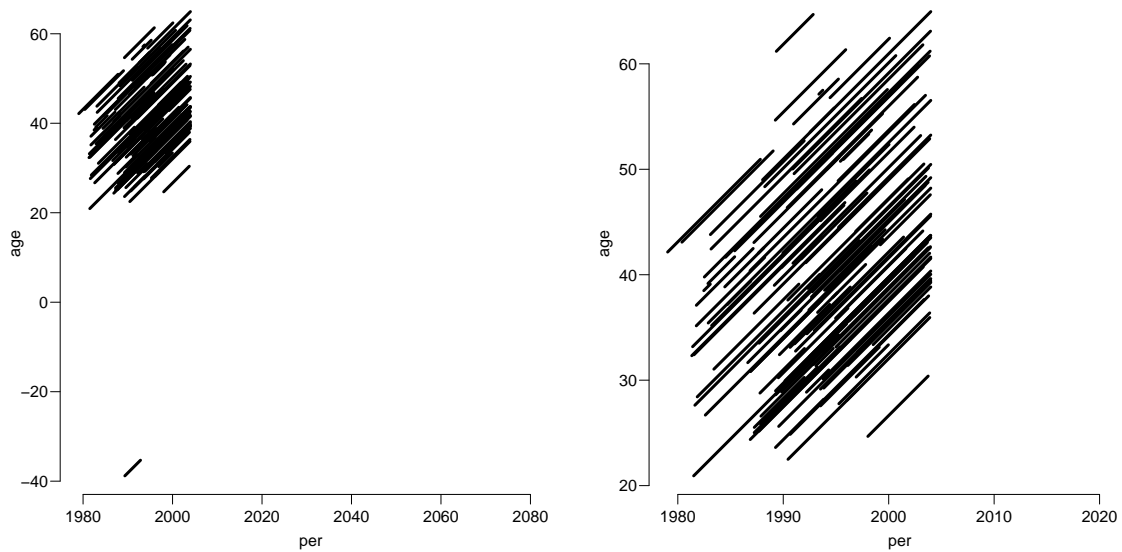


Figure 2.8: *Default Lexis diagram before and after correction of the obvious data outlier.*

```
pdf( "./graph/renal-Lexis-fancy.pdf", height=80/5+1, width=40/5+1 )
par( mai=c(3,3,1,1)/4, mgp=c(3,1,0)/1.6 )
plot( Lr, 1:2, col=c("blue","red")[Lr$sex], lwd=3, grid=0:20*5,
      xlab="Calendar time", ylab="Age",
      xlim=c(1970,2010), ylim=c(0,80), xaxs="i", yaxs="i", las=1 )
dev.off()

null device
      1
```

6. We now do a Cox-regression analysis with the variables sex and age at entry into the study, using time since entry to the study as time scale.

```
library( survival )
mc <- coxph( Surv( lex.dur, lex.Xst=="ESRD" ) ~
             I(age/10) + sex, data=Lr )
summary( mc )
```

Call:
coxph(formula = Surv(lex.dur, lex.Xst == "ESRD") ~ I(age/10) + sex, data = Lr)

n= 125, number of events= 77

	coef	exp(coef)	se(coef)	z	Pr(> z)
I(age/10)	0.5514	1.7357	0.1402	3.932	8.43e-05 ***
sexF	-0.1817	0.8338	0.2727	-0.666	0.505

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
I(age/10)	1.7357	0.5761	1.3186	2.285
sexF	0.8338	1.1993	0.4886	1.423

Concordance= 0.612 (se = 0.036)

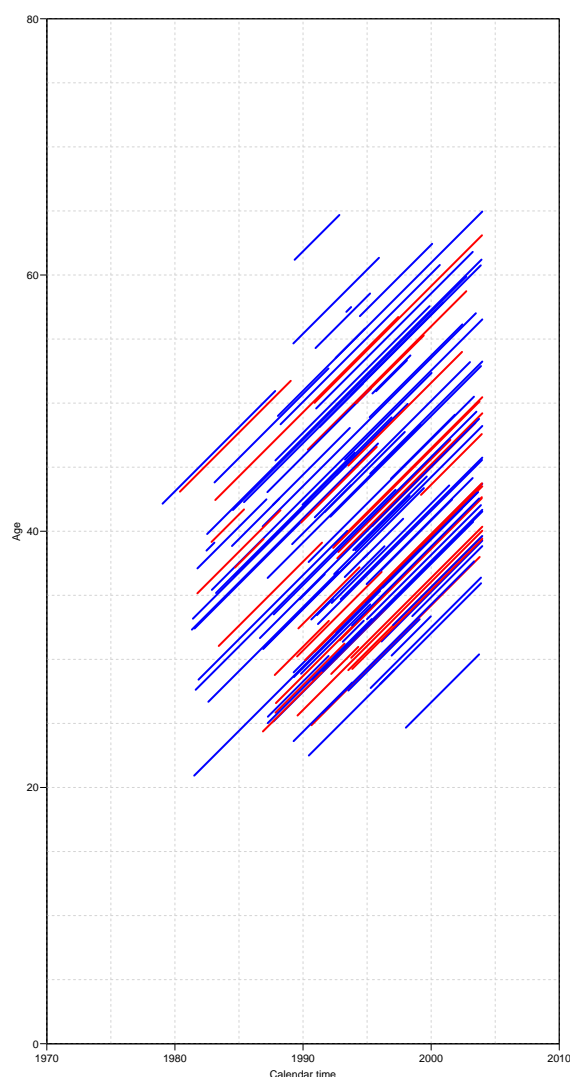


Figure 2.9: *The more fancy version of the Lexis diagram for the renal data.*

```
Likelihood ratio test= 16.07 on 2 df, p=3e-04
Wald test             = 16.38 on 2 df, p=3e-04
Score (logrank) test = 16.77 on 2 df, p=2e-04
```

The hazard ratio between males and females is 1.19 (0.70–2.04) (the inverse of the c.i. for female vs male) and between two persons who differ 10 years in age at entry it is 1.74 (1.32–2.29).

7. The main focus of the paper was to assess whether the occurrence of remission (return to a lower level of albumin excretion, an indication of kidney recovery) influences mortality. “Remission” is a time-dependent variable which is initially 0, but takes the value 1 when remission occurs. This is accomplished using the `cutLexis` function on the `Lexis` object, where we introduce a remission state “Rem”. We declare the “NRA” state as a precursor state, i.e. a state that is *less* severe than “Rem” in the sense that a person who see a remission will stay in the “Rem” state unless he goes to the “ESRD” state. The statement to do this is:


```
Lc <- cutLexis( Lr, cut = Lr$dor, # where to cut follow up
               timescale = "per", # what timescale are we referring to
               new.state = "Rem", # name of the new state
               split.state = TRUE, # different states depending on previous
               precursor.states = "NRA" ) # which states are less severe
summary( Lc )
```

Transitions:

From	NRA	Rem	ESRD	ESRD(Rem)	Records:	Events:	Risk time:	Persons:
NRA	24	29	69	0	122	98	824.77	122
Rem	0	24	0	8	32	8	259.90	32
Sum	24	53	69	8	154	106	1084.67	125

Note that we have two different ESRD states depending on whether the person was in remission or not at the time of ESRD.

To illustrate how the cutting of follow-up has worked we can list the records for select persons before and after the split:

```
subset( Lr, lex.id %in% c(2:4,21) )[,c(1:9,12)]
```

lex.id	per	age	tfr	lex.dur	lex.Cst	lex.Xst	id	sex	dor
2	1989.53	30.23	0	6.60	NRA	ESRD	26	F	1989.814
3	1987.85	25.83	0	5.39	NRA	ESRD	27	F	NA
4	1995.24	44.50	0	8.75	NRA	NRA	33	M	1995.717
21	1992.95	32.36	0	0.08	NRA	NRA	152	F	NA

```
subset( Lc, lex.id %in% c(2:4,21) )[,c(1:9,12)]
```

lex.id	per	age	tfr	lex.dur	lex.Cst	lex.Xst	id	sex	dor
2	1989.53	30.23	0.00	0.28	NRA	Rem	26	F	1989.814
2	1989.81	30.51	0.28	6.32	Rem	ESRD(Rem)	26	F	1989.814
3	1987.85	25.83	0.00	5.39	NRA	ESRD	27	F	NA
4	1995.24	44.50	0.00	0.47	NRA	Rem	33	M	1995.717
4	1995.72	44.97	0.47	8.28	Rem	Rem	33	M	1995.717
21	1992.95	32.36	0.00	0.08	NRA	NRA	152	F	NA

8. We can show how the states are connected and the number of transitions between them by using `boxes`. This is an interactive command that requires you to click in the graph window

Alternatively you can let R try to place the boxes for you, and even compute rates (in this case in units of events per 100 PY):

```
boxes(Relevel(Lc, c(1,2,4,3)),
      boxpos = TRUE, scale.R = 100, show.BE = TRUE)
```

9. We can make a Lexis diagram where different coloring is used for different segments of the follow-up. The `plot.Lexis` function draws a line for each record in the dataset, so we can just index the coloring by `lex.Cst` and `lex.Xst` as appropriate — indexing by a factor corresponds to indexing by the *index number* of the factor levels, so you must be know which order the factor levels are in.

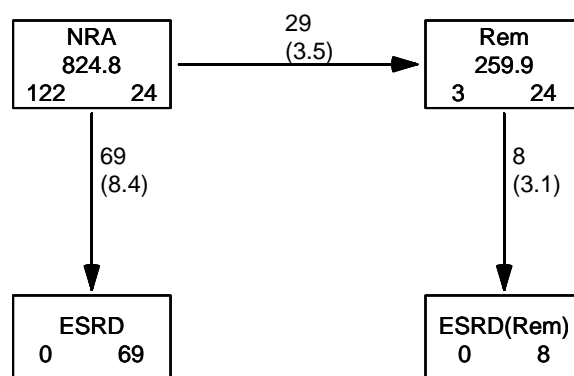


Figure 2.10: States and transitions between them.

The numbers in each box are the person-years and the number of persons starting (left) and ending (right) their follow-up in each state; the numbers on the arrows are the number of transitions and the overall transition rates (in per 100 PY, by the `scale.R=100`).

```

par( mai=c(3,3,1,1)/4, mgp=c(3,1,0)/1.6 )
plot( Lc, col=c("red","limegreen")[Lc$lex.Cst],
      xlab="Calendar time", ylab="Age",
      lwd=3, grid=0:20*5, xlim=c(1970,2010), ylim=c(0,80), xaxs="i", yaxs="i", las=1 )
points( Lc, pch=c(NA,NA,16,16)[Lc$lex.Xst],
        col=c("red","limegreen","transparent")[Lc$lex.Cst])
points( Lc, pch=c(NA,NA,1,1)[Lc$lex.Xst],
        col="black", lwd=2 )

```

10. We now make Cox-regression of mortality (i.e. endpoint “ESRD”) with sex, age at entry and remission as explanatory variables, using time since entry as timescale.

We include `lex.Cst` as time-dependent variable, and indicate that each record represents follow-up from `tfi` to `tfi+lex.dur`.

```

( EP <- levels(Lc)[3:4] )
[1] "ESRD"      "ESRD(Rem)"

m1 <- coxph( Surv( tfi,                # from
                  tfi+lex.dur,         # to
                  lex.Xst %in% EP ) ~  # event
             sex + I((doe-dob-50)/10) + # fixed covariates
             (lex.Cst=="Rem"),          # time-dependent variable
             data = Lc )
summary( m1 )

```

Call:

```

coxph(formula = Surv(tfi, tfi + lex.dur, lex.Xst %in% EP) ~ sex +
      I((doe - dob - 50)/10) + (lex.Cst == "Rem"), data = Lc)

```

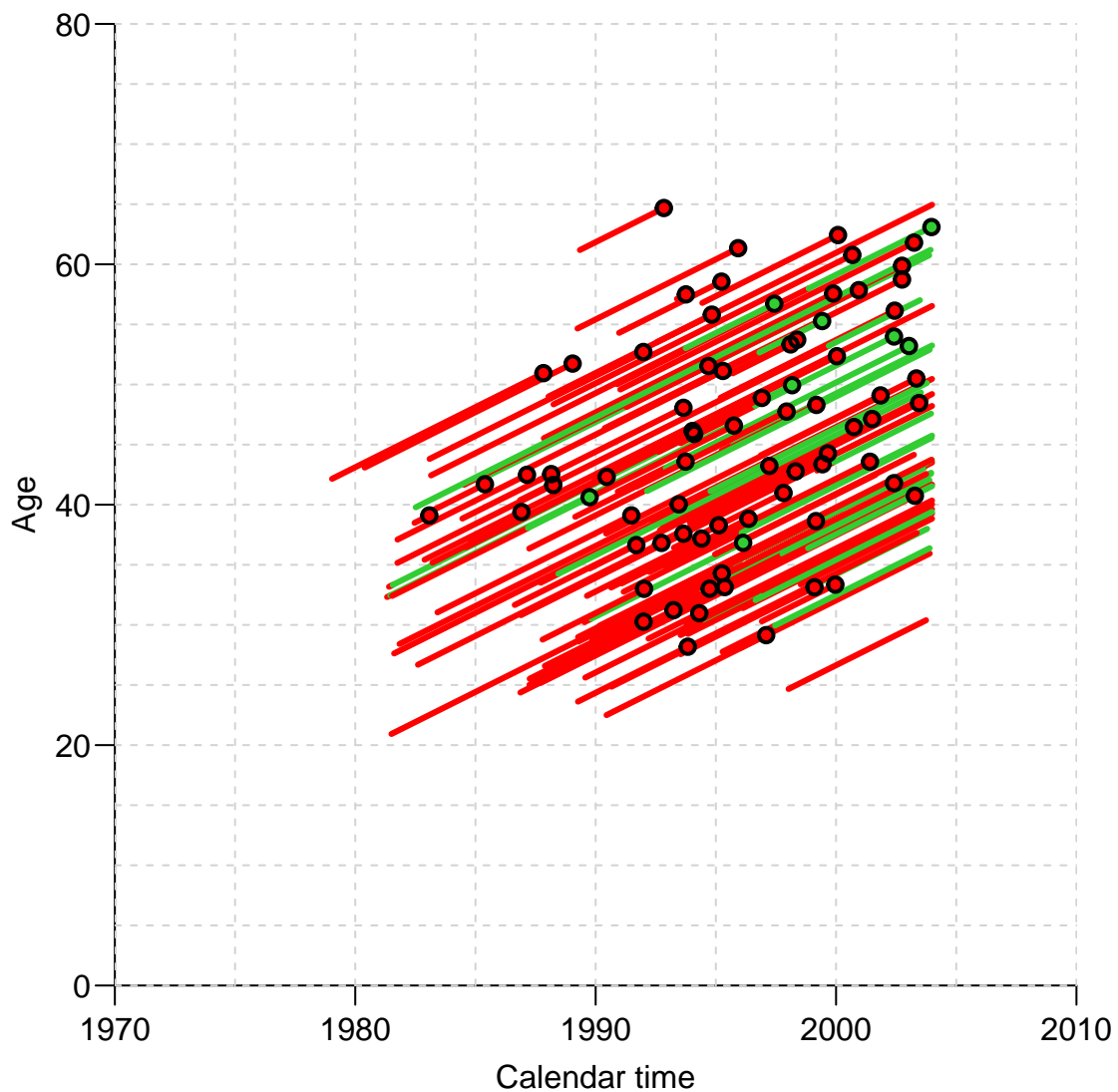


Figure 2.11: *Lexis diagram for the split data, where time after remission is shown in green.*

```
n= 154, number of events= 77
```

	coef	exp(coef)	se(coef)	z	Pr(> z)
sexF	-0.05534	0.94616	0.27500	-0.201	0.840517
I((doe - dob - 50)/10)	0.52190	1.68522	0.13655	3.822	0.000132 ***
lex.Cst == "Rem"TRUE	-1.26241	0.28297	0.38483	-3.280	0.001036 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

	exp(coef)	exp(-coef)	lower .95	upper .95
sexF	0.9462	1.0569	0.5519	1.6220
I((doe - dob - 50)/10)	1.6852	0.5934	1.2895	2.2024
lex.Cst == "Rem"TRUE	0.2830	3.5339	0.1331	0.6016

Concordance= 0.664 (se = 0.033)
Likelihood ratio test= 30.31 on 3 df, p=1e-06
Wald test = 27.07 on 3 df, p=6e-06

```
Score (logrank) test = 29.41 on 3 df, p=2e-06
```

We see that the rate of ESRD is less than a third among those who obtain remission — 0.28 (0.13–0.60), showing that we can be pretty sure that the rate is at least halved.

2.17.2 Splitting the follow-up time

11. We split the follow-up time every month after entry, and verify that the number of events and risk time is the same as before and after the split:

```
sLc <- splitLexis( Lc, "tfi", breaks=seq(0,30,1/12) )
summary( Lc, scale=100 )
```

Transitions:

From	To	NRA	Rem	ESRD	ESRD(Rem)	Records:	Events:	Risk time:	Persons:
NRA	24	29	69	0	122	98	8.25	122	
Rem	0	24	0	8	32	8	2.60	32	
Sum	24	53	69	8	154	106	10.85	125	

```
summary(sLc, scale=100 )
```

Transitions:

From	To	NRA	Rem	ESRD	ESRD(Rem)	Records:	Events:	Risk time:	Persons:
NRA	9854	29	69	0	9952	98	8.25	122	
Rem	0	3139	0	8	3147	8	2.60	32	
Sum	9854	3168	69	8	13099	106	10.85	125	

Thus both the cutting and splitting preserves the number of ESRD events and the person-years. The cut added the “Rem” events, but these were preserved by the splitting.

12. Now we fit the Poisson-model corresponding to the Cox-model we fitted previously. The function `Ns()` produces a model matrix corresponding to a piece-wise cubic function, modeling the baseline hazard explicitly (think of the `Ns` terms as the baseline hazard that is not visible in the Cox-model)

```
mp <- glm.Lexis(sLc, ~ Ns(tfi, knots = c(0,2,5,10)) +
  sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"))
```

stats::glm Poisson analysis of Lexis object sLc with log link:
Rates for transitions:
NRA->ESRD
Rem->ESRD(Rem)

```
ci.exp( mp )
```

	exp(Est.)	2.5%	97.5%
(Intercept)	0.01664432	0.003956666	0.07001685
Ns(tfi, knots = c(0, 2, 5, 10))1	5.18917655	1.949197027	13.81469029
Ns(tfi, knots = c(0, 2, 5, 10))2	34.20004199	1.764818735	662.75524463
Ns(tfi, knots = c(0, 2, 5, 10))3	4.43318269	2.179977108	9.01528219
sexF	0.91751162	0.536258443	1.56981691
I((doe - dob - 40)/10)	1.70082390	1.300813859	2.22384004
I(lex.Cst == "Rem")TRUE	0.27927558	0.131396852	0.59358233

We see that the effects are pretty much the same as from the Cox-model.

13. We may instead use the `gam` function from the `mgcv` package. There is convenience wrapper for this as well:

```
library( mgcv )
mx <- gam.Lexis(sLc,
               ~ s(tfi, k=10) + sex + I((doe-dob-40)/10) + I(lex.Cst=="Rem"))

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for transitions:
NRA->ESRD
Rem->ESRD(Rem)

ci.exp( mp, subset=c("Cst","dob","sex") )

               exp(Est.)      2.5%      97.5%
I(lex.Cst == "Rem")TRUE 0.2792756 0.1313969 0.5935823
I((doe - dob - 40)/10)  1.7008239 1.3008139 2.2238400
sexF                    0.9175116 0.5362584 1.5698169

ci.exp( mx, subset=c("Cst","dob","sex") )

               exp(Est.)      2.5%      97.5%
I(lex.Cst == "Rem")TRUE 0.2784659 0.1309446 0.5921838
I((doe - dob - 40)/10)  1.6992069 1.2995225 2.2218192
sexF                    0.9309945 0.5435486 1.5946150
```

We see that there is virtually no difference between the two approaches in terms of the regression parameters.

14. We extract the regression parameters from the models using `ci.exp` and compare with the estimates from the Cox-model:

```
ci.exp( mx, subset=c("sex","dob","Cst"), pval=TRUE )

               exp(Est.)      2.5%      97.5%      P
sexF          0.9309945 0.5435486 1.5946150 0.7945394004
I((doe - dob - 40)/10) 1.6992069 1.2995225 2.2218192 0.0001066910
I(lex.Cst == "Rem")TRUE 0.2784659 0.1309446 0.5921838 0.0008970863

ci.exp( m1 )

               exp(Est.)      2.5%      97.5%
sexF          0.9461646 0.5519334 1.621985
I((doe - dob - 50)/10) 1.6852196 1.2895097 2.202360
lex.Cst == "Rem"TRUE  0.2829710 0.1330996 0.601599

round( ci.exp( mp, subset=c("sex","dob","Cst") ) / ci.exp( m1 ), 3 )

               exp(Est.)  2.5% 97.5%
sexF          0.970 0.972 0.968
I((doe - dob - 40)/10)  1.009 1.009 1.010
I(lex.Cst == "Rem")TRUE  0.987 0.987 0.987
```

Thus we see that it has an absolute minimal influence on the regression parameters to impose the assumption of smoothly varying rates or not.

15. The model has the same assumptions as the Cox-model about proportionality of rates, but there is an additional assumption that the hazard is a smooth function of time since entry. It seems to be a sensible assumption (well, restriction) to put on the rates that they vary smoothly by time. No such restriction is made in the Cox model. The `gam` model optimizes the shape of the smoother by general cross-validation:

```
plot( mx )
```

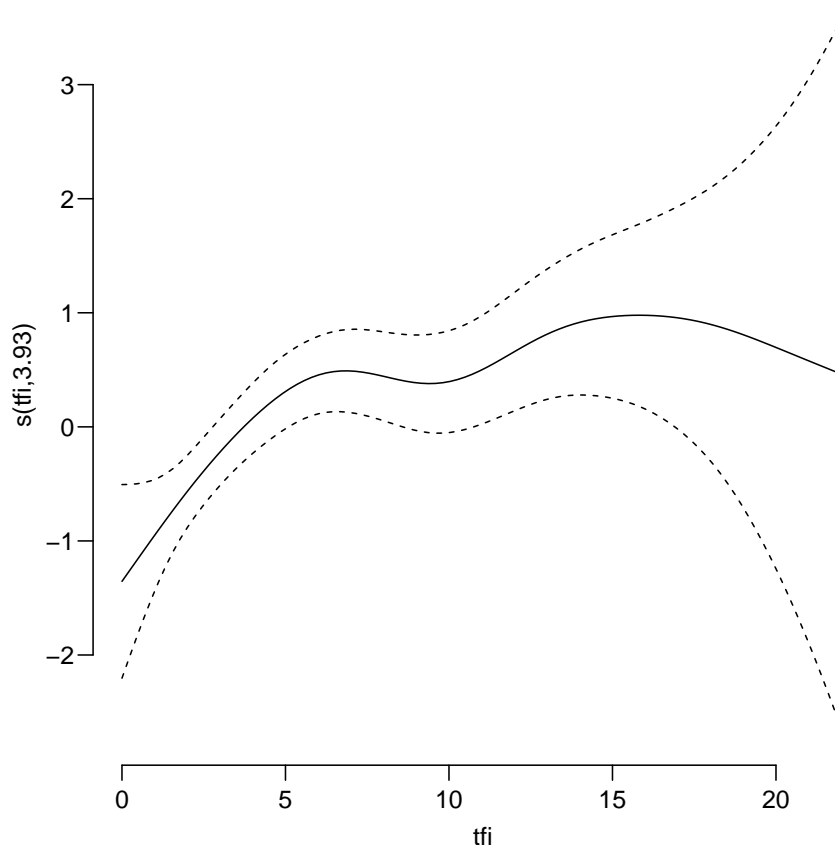


Figure 2.12: *Estimated non-linear effect of tfi as estimated by gam.*

16. However, `plot` does not give you the *absolute* level of the underlying rates because it bypasses the intercept. If we want this we can predict the rates as a function of the covariates:

```
nd <- data.frame( tfi = seq(0,20,.1),
                  sex = "M",
                  doe = 1990,
                  dob = 1940,
                  lex.Cst = "NRA")
str(nd)
'data.frame':      201 obs. of  5 variables:
 $ tfi      : num  0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 ...
 $ sex      : chr  "M" "M" "M" "M" ...
 $ doe      : num  1990 1990 1990 1990 1990 1990 1990 1990 1990 1990 ...
 $ dob      : num  1940 1940 1940 1940 1940 1940 1940 1940 1940 1940 ...
 $ lex.Cst  : chr  "NRA" "NRA" "NRA" "NRA" ...
```

```

matshade(nd$tfi, cbind(ci.pred(mp, newdata = nd),
                      ci.pred(mx, newdata = nd)) * 100,
        plot = TRUE,
        type="l", lwd = 3:4, col = c("black", "forestgreen"),
        log = "y", xlab = "Time since entry (years)",
        ylab = "ESRD rate (per 100 PY) for 50 year man")

```



Figure 2.13: Rates of ESRD by time since NRA for a man aged 50 at start of NRA. The green line is the curve fitted by *gam*, the black the one fitted by an ordinary *glm* using *Ns* with knots at 0, 2, 5 and 10 years.

2.17.3 Prediction from the multistate model

If we want to make proper statements about the survival and disease probabilities we must know not only how the occurrence of remission influences the rate of death/ESRD, but we must also model the occurrence rate of remission itself.

17. The rates of ESRD were modelled by a Poisson model with effects of age and time since NRA — in the models *mp* and *mx*. But if we want to model whole process we must also model the remission rates transition from “NRA” to “Rem”, but the number of events is rather small (see figure 2.10), so we restrict covariates in this model to only time since NRA and sex. Note that only the records that relate to the “NRA” state can be used; this is done with the *from* argument to *gam.Lexis*:

```

mr <- gam.Lexis(sLc, ~ s( tfi, k=10 ) + sex,
               from = "NRA",
               to = "Rem")

mgcv::gam Poisson analysis of Lexis object sLc with log link:
Rates for the transition:
NRA->Rem

ci.exp(mr, pval = TRUE)

```

	exp(Est.)	2.5%	97.5%	P
(Intercept)	0.02466177	0.01486719	0.04090905	1.254086e-46
sexF	2.60619252	1.25503371	5.41199761	1.019157e-02
s(tfi).1	1.00756081	0.83823640	1.21108889	9.360463e-01
s(tfi).2	0.99578104	0.81097748	1.22269718	9.678018e-01
s(tfi).3	0.99740759	0.89841258	1.10731073	9.611811e-01
s(tfi).4	1.00231534	0.89552909	1.12183519	9.679048e-01
s(tfi).5	0.99773836	0.90957003	1.09445321	9.617435e-01
s(tfi).6	0.99775106	0.90656107	1.09811376	9.632777e-01
s(tfi).7	1.00244317	0.91723283	1.09556950	9.570639e-01
s(tfi).8	0.99404123	0.69737098	1.41691870	9.736371e-01
s(tfi).9	0.94790708	0.63364240	1.41803616	7.946051e-01

We see that there is a clear effect of sex; women have a remission rate 2.6 times higher than for men.

18. In order to use the function `simLexis` we must have as input to this the initial status of the persons whose life-course we shall simulate, and the transition rates in suitable form:

- Suppose we want predictions for men aged 50 at NRA. The input is in the form of a `Lexis` object (where `lex.dur` and `lex.Xst` will be ignored). Note that in order to carry over the `time.scales` and the `time.since` attributes, we construct the input object using `subset` to select columns, and `NULL` to select rows (see the example in the help file for `simLexis`):

```

inL <- subset( sLc, select=1:11 )[NULL,]
str( inL )
Classes 'Lexis' and 'data.frame':      0 obs. of  11 variables:
 $ lex.id : int
 $ per    : num
 $ age    : num
 $ tfi    : num
 $ lex.dur: num
 $ lex.Cst: Factor w/ 4 levels "NRA","Rem","ESRD",...
 $ lex.Xst: Factor w/ 4 levels "NRA","Rem","ESRD",...
 $ id     : num
 $ sex    : Factor w/ 2 levels "M","F":
 $ dob    : num
 $ doe    : num
 - attr(*, "time.scales")= chr [1:3] "per" "age" "tfi"
 - attr(*, "time.since")= chr [1:3] "" "" ""
 - attr(*, "breaks")=List of 3
 ..$ per: NULL
 ..$ age: NULL
 ..$ tfi: num [1:361] 0 0.0833 0.1667 0.25 0.3333 ...
timeScales(inL)
[1] "per" "age" "tfi"

```



```

inL[1,"lex.id"] <- 1
inL[1,"per"] <- 2000
inL[1,"age"] <- 50
inL[1,"tfi"] <- 0
inL[1,"lex.Cst"] <- "NRA"
inL[1,"lex.Xst"] <- NA
inL[1,"lex.dur"] <- NA
inL[1,"sex"] <- "M"
inL[1,"doe"] <- 2000
inL[1,"dob"] <- 1950
inL <- rbind( inL, inL )
inL[2,"sex"] <- "F"
inL

lex.id  per age tfi lex.dur lex.Cst lex.Xst id sex  dob  doe
      1 2000  50   0      NA      NRA   <NA> NA   M 1950 2000
      1 2000  50   0      NA      NRA   <NA> NA   F 1950 2000

str( inL )
Classes 'Lexis' and 'data.frame':      2 obs. of  11 variables:
 $ lex.id : num  1 1
 $ per    : num  2000 2000
 $ age    : num  50 50
 $ tfi    : num  0 0
 $ lex.dur: num  NA NA
 $ lex.Cst: Factor w/ 4 levels "NRA","Rem","ESRD",...: 1 1
 $ lex.Xst: Factor w/ 4 levels "NRA","Rem","ESRD",...: NA NA
 $ id     : num  NA NA
 $ sex    : Factor w/ 2 levels "M","F": 1 2
 $ dob    : num  1950 1950
 $ doe    : num  2000 2000
- attr(*, "breaks")=List of 3
 ..$ per: NULL
 ..$ age: NULL
 ..$ tfi: num [1:361] 0 0.0833 0.1667 0.25 0.3333 ...
- attr(*, "time.scales")= chr [1:3] "per" "age" "tfi"
- attr(*, "time.since")= chr [1:3] "" "" ""

```

- The other input for the simulation is the transitions, which is a list with an element for each transient state (that is “NRA” and “Rem”), each of which is again a list with names equal to the states that can be reached from the transient state. The content of the list will be `glm` objects, in this case the models we just fitted, describing the transition rates:

```

Tr <- list("NRA" = list("Rem"      = mr,
                        "ESRD"     = mx ),
          "Rem"  = list("ESRD(Rem)" = mx))

```

19. Now generate the life course of 5,000 persons (of each sex), and look at the summary. The `system.time` command is just to tell you how long it took, you may want to start with 100 just to see how long that takes.

```

system.time( sM <- simLexis( Tr, inL, N=5000 ) )

user  system elapsed
47.191   7.570  39.703

# save( sM, file="sM.Rda" )
# load(      file="sM.Rda" )
summary( sM, by="sex" )

```

\$M

Transitions:

	To							
From	NRA	Rem	ESRD	ESRD(Rem)	Records:	Events:	Risk time:	Persons:
NRA	19	703	4278	0	5000	4981	27991.28	5000
Rem	0	206	0	497	703	497	7225.96	703
Sum	19	909	4278	497	5703	5478	35217.24	5000

\$F

Transitions:

	To							
From	NRA	Rem	ESRD	ESRD(Rem)	Records:	Events:	Risk time:	Persons:
NRA	11	1636	3353	0	5000	4989	24767.70	5000
Rem	0	511	0	1125	1636	1125	16861.36	1636
Sum	11	2147	3353	1125	6636	6114	41629.06	5000

The many ESRD-events in the resulting data set is attributable to the fact that we simulate for a very long follow-up time.

20. Now we want to count how many persons are present in each state at each time for the first 10 years after entry (which is at age 50). This can be done by using `nState`:

```
nStm <- nState( subset(sM,sex=="M"), at=seq(0,10,0.1), from=50, time.scale="age" )
nStf <- nState( subset(sM,sex=="F"), at=seq(0,10,0.1), from=50, time.scale="age" )
head( nStf )
```

	State			
when	NRA	Rem	ESRD	ESRD(Rem)
50	5000	0	0	0
50.1	4932	49	19	0
50.2	4877	83	39	1
50.3	4834	104	61	1
50.4	4781	136	82	1
50.5	4727	163	109	1

We see that we get a count of persons in each state at time points 0,0.1,0.2,... years after 50 on the age time scale.

21. Once we have the counts of persons in each state at the designated time points, we compute the cumulative fraction over the states, arranged in order given by `perm`:

```
ppm <- pState( nStm, perm=c(2,1,3,4) )
ppf <- pState( nStf, perm=c(2,1,3,4) )
head( ppf )
```

	State			
when	Rem	NRA	ESRD	ESRD(Rem)
50	0.0000	1.0000	1.0000	1
50.1	0.0098	0.9962	1.0000	1
50.2	0.0166	0.9920	0.9998	1
50.3	0.0208	0.9876	0.9998	1
50.4	0.0272	0.9834	0.9998	1
50.5	0.0326	0.9780	0.9998	1

```
tail( ppf )
```

	State			
when	Rem	NRA	ESRD	ESRD(Rem)
59.5	0.2168	0.3328	0.9108	1
59.6	0.2170	0.3302	0.9102	1
59.7	0.2158	0.3270	0.9086	1
59.8	0.2158	0.3242	0.9076	1
59.9	0.2156	0.3218	0.9070	1
60	0.2142	0.3186	0.9050	1

22. Then we plot the cumulative probabilities using the `plot` method for `pState` objects:

```
plot( ppf )
```

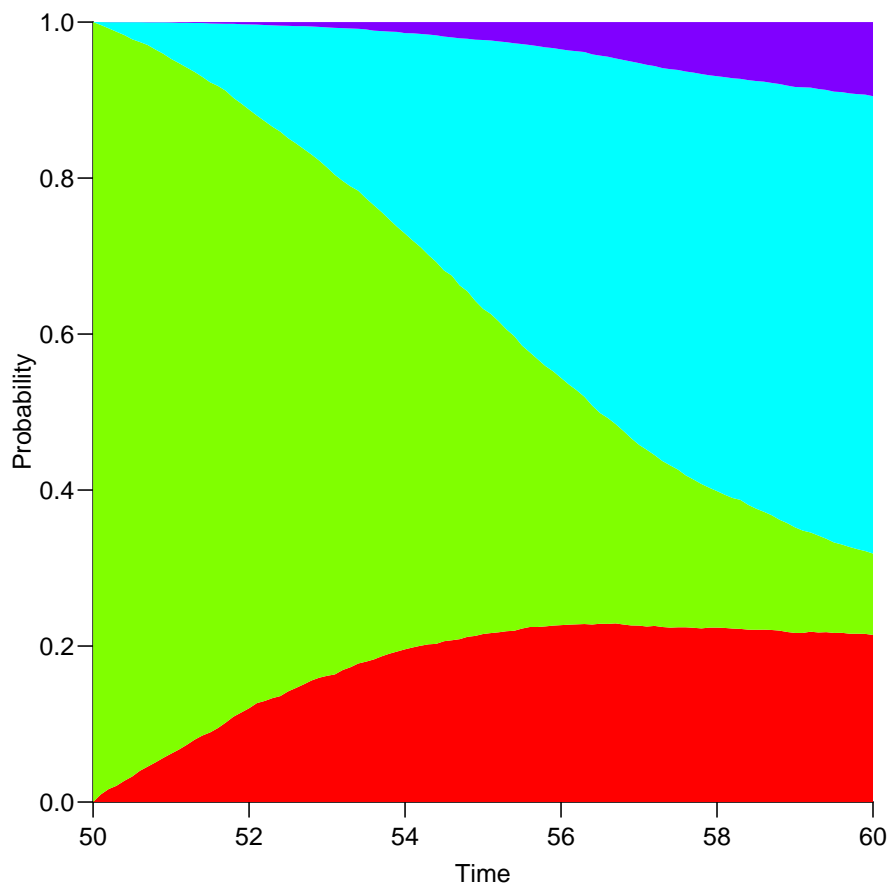


Figure 2.14: The default plot for a `pState` object, bottom to top: Alive remission, alive no remission, dead no remission, dead remission.

23. Now try to improve the plot so that it is easier to read, and easier to compare men and women:

```
par( mfrow=c(1,2), mar=c(3,1.5,1,1), oma=c(0,2,0,0), las=1 )
#
plot( ppm, col=c("limegreen","red","#991111","forestgreen") )
mtext( "Probability", side=2, las=0, outer=T, line=0.5 )
lines( as.numeric(rownames(ppm)), ppm[, "NRA"], lwd=4 )
text( 59.5, 0.95, "Men", adj=1, col="white", font=2, cex=1.2 )
```

```

axis( side=4, at=0:10/10 )
axis( side=4, at=0:20/20 , labels=NA, tck=-0.02 )
axis( side=4, at=1:99/100, labels=NA, tck=-0.01 )
#
plot( ppf, col=c("limegreen","red","#991111","forestgreen"),
      xlim=c(60,50), yaxt="n", ylab="" )
lines( as.numeric(rownames(ppf)), ppf[, "NRA"], lwd=4 )
text( 59.5, 0.95, "Women", adj=0, col="white", font=2, cex=1.2 )
axis( side=2, at=0:10/10 , labels=NA )
axis( side=2, at=0:20/20 , labels=NA, tck=-0.02 )
axis( side=2, at=1:99/100, labels=NA, tck=-0.01 )

```

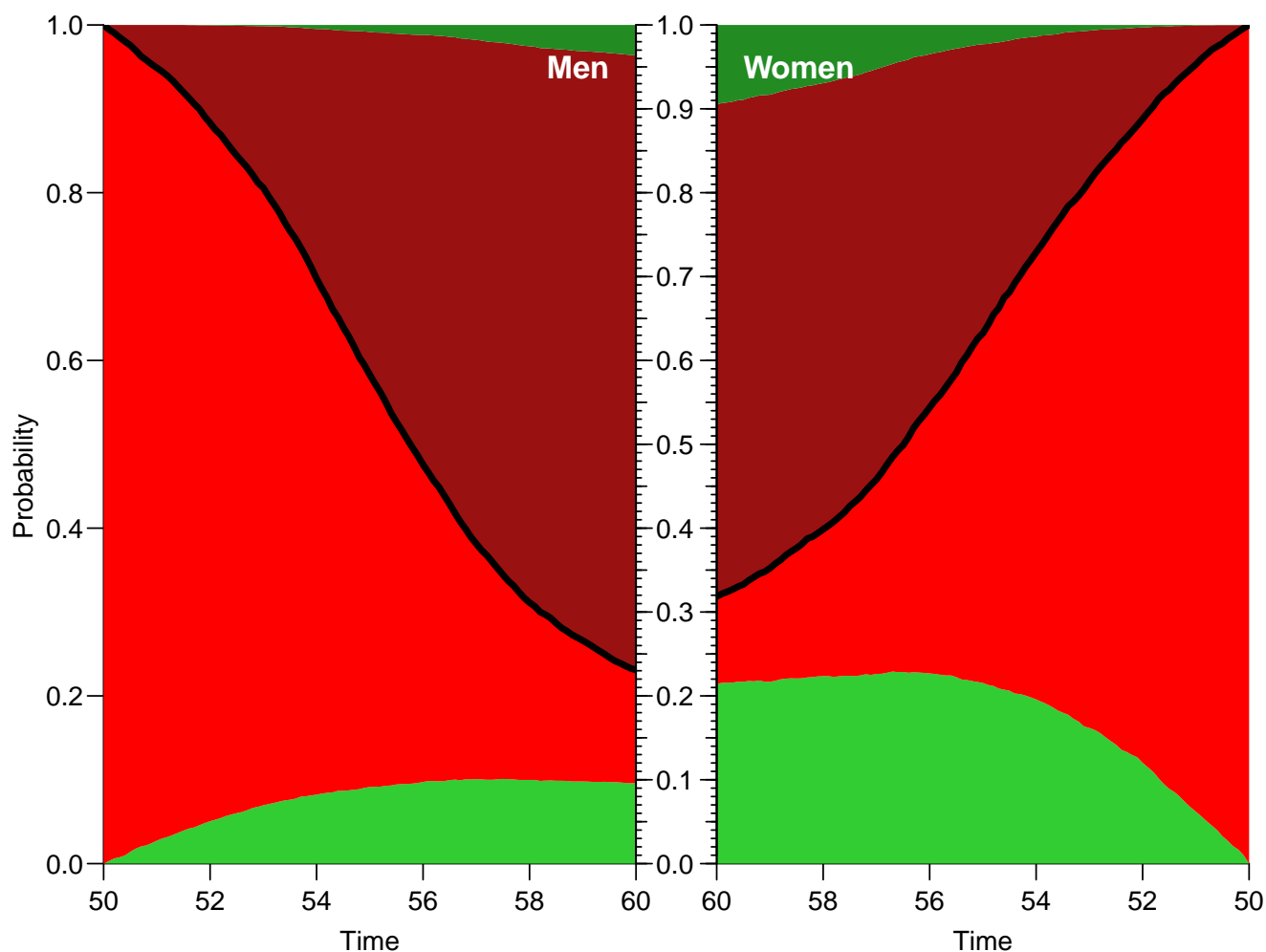


Figure 2.15: Predicted state occupancy for men and women entering at age 50. The green areas are remission, the red without remission; the black line is the survival curve.

We see that the probability that a 50-year old man with NRA sees a remission from NRA during the next 10 years is about 25% whereas the same for a woman is about 50%. Also it is apparent that no new remissions occur after about 5 years since NRA — mainly because only persons with remission are alive after 5 years.