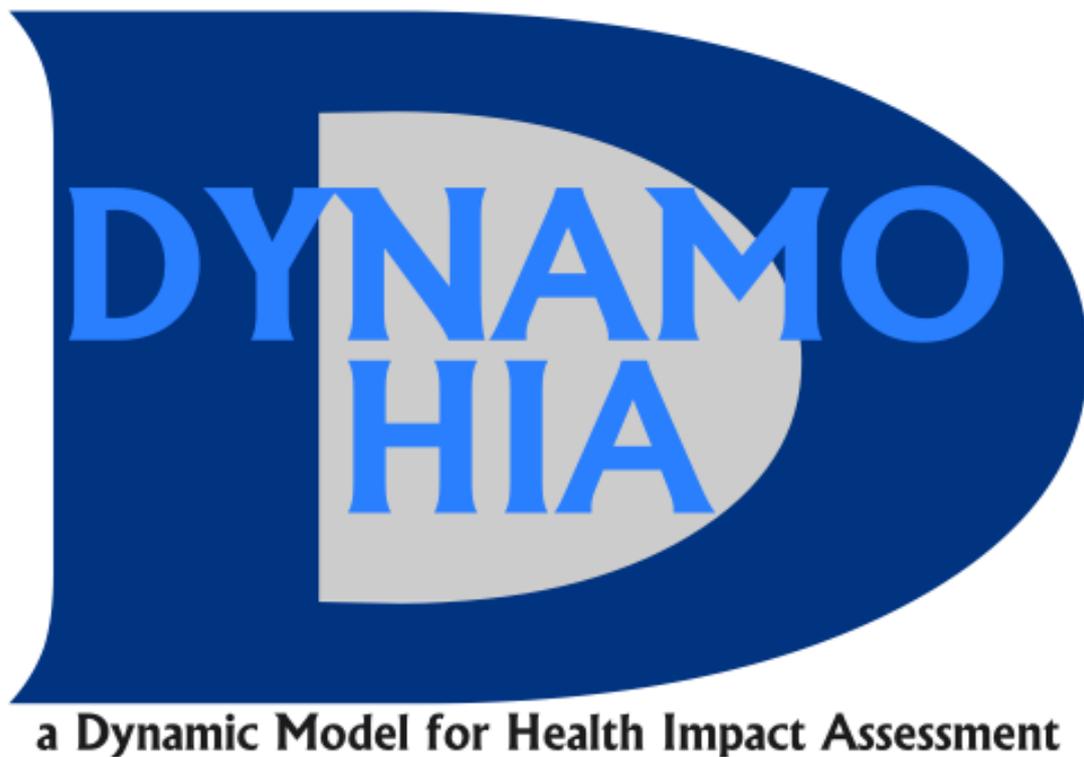


DYNAMO-HIA

A Dynamic Model for Health Impact Assessment

USER GUIDE AND MANUAL

Version 2.0.8



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DYNAMO-HIA – A short Introduction

The document gives an overview about how to use DYNAMO, what it can do and how it works.

We combine this introduction with a practical tutorial using real life data.

Overview

DYNAMO-HIA (DYNAmic MOdeling for Health Impact Assessment) is a generic software tool specially designed to aid the quantification step in health impact assessment. DYNAMO-HIA is generic in the sense that it allows arbitrary chronic diseases or risk-factors that fit the standard causal pathway of the health impact assessment framework to be modeled. The user can import and use his or her own data to add and analyze diseases or populations that are of interest to him or her.

DYNAMO-HIA has been specifically designed to quantify the impact of user-specified risk-factor changes due to policy or interventions on various and multiple diseases on overall population health. Using a Markov-based modeling approach that allows for explicit risk-factor states, it dynamically simulates a real-life population. A built-in parameter estimation module ensures that only standard epidemiological evidence, i.e. data on incidence, prevalence, and mortality are required. DYNAMO-HIA provides a rich model output of summary measures -- such as life expectancy and disease-free life expectancy -- and detailed data -- such as mortality/survival rates and prevalence numbers -- by age, sex, and risk-factor status over time.

This manual gives an introduction in how to use DYNAMO-HIA. The prototype version of DYNAMO-2 is accompanied with an example data set in the “Tutorial_Data” directory. In this manual we refer several times to this data set using it as step-by-step tutorial to describe the different options of DYNAMO.

Changes in DYNAMO-2 compared to DYNAMO-1

Changed INPUT formats.

DYNAMO-1 was build to work with DALY-weights, DYNAMO-2 to work with percentage disability. Although technically the difference is mainly in the interpretation, the terminology in the interface has been changed from DALY-weight to disability.

This means that the **old input directories will no longer work.**

In order to use old DYNAMO-HIA-1 directories with DYNAMO-HIA 2, the following changes are needed:

1. (to be made with Microsoft explorer)

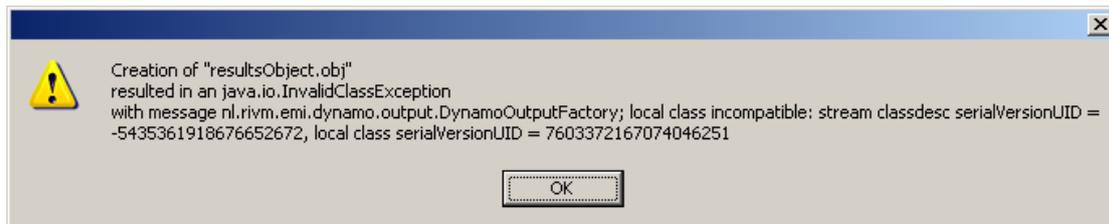
In the **Diseases** directory the directoryname DALY_weights needs to be changed to Disability. Note: This should start with a capital, but further be lower case.

In the **Populations** directory the file overalldalyweights.xml must be rename into overalldisability.xml, and this file also needs to be edited (for instance with wordpad) in order to change the labels <overalldalyweights> and </overalldalyweights> into <overalldisability> and </overalldisability>.

Also the **simulation** configuration file (configuration.xml) has a slightly different format, but usually this will not result in errors.

Changed output object

The output object is changed, so old output objects can no longer be read and an attempt to open the object will result in the following message:



New in DYNAMO-HIA-2

Disability and disability free life expectancy as outcomes

DYNAMO-HIA-2 includes the following output with disability:

- Population pyramid with subdivision according to presence/absence of disability
- Prevalence of disability by risk class and gender
- life expectancy with and life expectancy without disability (cohort en Sullivan)

Disability can depend on the risk factor

The user now can specify a dependency of disability on the risk factor. To do this, you must:

- give an odds ratio on disability for the risk factor (in the risk factor part of the reference data)
- specify that you want to use this odds ratio on the tabfolder “relative risks” in the simulation screen

When running the model, DYNAMO will let the disability depend on the risk factor status, maintaining the overall level of as specified for the total population at the start of the simulation.

Similar to mortality, if the sum of disease-specific disability across all modeled diseases in a particular risk factor class exceeds total disability, total disability is leading and the program will not run with such data. An error message is given when this occurs.

Intermediate disability parameters visible

In the parameter directory the intermediate parameters for disability are added.

Incidence.

The average annual incidence now is also part of the output. (at the moment only implemented for categorical risk factors)

DALY-calculations.

In the life-expectancy screen there is now also an option to calculate a DALY-type difference between scenarios. In this option, the scenario is only applied during the first year; after this first year the risk factor values return to the value it would have had after one year in the reference scenario.

Extra survival, mortality and number in population plots

These plots are now also available by risk factor level

Extra output files

All output files now can also be requested in csv format. Also a file containing all possible life expectancy measures can be requested.

Other changes

Treatment of higher disease-specific than overall disability

When the sum of disease-specific disability across all modeled diseases exceeds total disability (in all risk factor classes together), the model gives an error message and asks the user to provide new data. This change was made because it was decided that total disability is leading. The previous version of DYNAMO in that case would use the higher disability specified for the diseases.

Bugfixes

Bugfix in the survival plot (application of success rate to different ages not correct: was applied)

Zero DALY-overall disability weights did not work in the old version, this has been fixed

Directories with // in the path, or some other non-alphanumeric symbols in the pathname did not work in the old version. This has been fixed

The handling of new-borns in scenarios with different transitions as the reference scenario was not consistent with that of scenarios with different initial prevalences. This

now is consistent. All newborns in the alternative scenario immediately get the prevalence belonging with the alternative scenario.

In the old version, there was an error when a continuous risk factor was created with only a single cut-off value: in that case no cut-off values could be specified, and the program proceeded as if 0 cut-off values were given. This was fixed.

Some writing errors in the excel readable files (year-based version only) were corrected.

The batch file now has a correct csv format (, as separator and . as decimal separator; this was: ; as separator and . as decimal separator).

In the module calculating nett transition rates, prevalence rates that did not exactly add up to 100% were corrected by adding or subtracting the remaining amount from the last category. In cases where the last category was empty this sometimes yielded negative prevalence rates, in which case the program would crash later on. This was solved by a more intelligent correction method.

Changes in DYNAMO-HIA-2 upto DYNAMO-HIA 2.0.8

New relative risk for other mortality for risk factor classes with zero prevalence

In earlier versions the relative risk for other mortality was set to 1 in risk factor classes with a prevalence of zero in the initial population. Up to version 2.04 such models with such empty risk factor classes mostly did not run when these risk classes were filled

during simulation (e.g. in an alternative scenario), so this relative risk was rarely used. However, from version 2.06 on the model was adapted to also run in this cases, and thus realistic relative risks are needed also in this case. These are provided from version 2.07. They calculated from the relative risk of mortality and expected increase in mortality due to excess mortality of risk factor related diseases in the same way as the relative risks of non-empty risk factor classes. Note that this change only affects simulations with 1) empty risk factor categories in the initial population that are filled in the simulation and 2) use a relative risk on all cause mortality .

New interpretation of zero population disability

When zero population disability is entered in combination with non-empty disease related disability, the program did not run before as the disease related disability needed to be smaller or equal to the population disability. In version 2.06 it is now assumed that zero population disability means that there is only disease related disability present. This option is only available when running from the interface, and not in the batch version.

Negative drift

From version 2.07 on the drift values supplied by the user can also be negative.

Bug fixes

In DYNAMO-2.07 the following bug-fixes were done:

Some files written from the interface were incomplete:

- In writing CVS (cohort data, single file), with the choice “separate for men and women” only data from men were included, while in the choice “total population” all records were written twice

- In writing cohort LE data, the life expectancies from age 95 were not included

These bugs have been removed.

Furthermore some error messages were reformulated to make them clearer

In version 2.0.8 a bug was fixed preventing the running of simulations with a continuous risk factor from the GUI. Furthermore the look of the life expectancy was changed back to the original look (in version 2.0.7 an update of the JFreeChart library had added a gradient to the graphs), and the shadow was removed from the population pyramid plot.

Furthermore the JAVA version was update to JAVA 8.

Installation

In the old version there were two ways to install the DYNAMO-HIA software: with an installer, and manually. Only the manual installation is offered for the new version, as in practice this option always worked, which was not the case for the installer

How to install by manual installation

Find the file DYNAMO-HIA-2.zip and unzip this to a suitable directory on your computer. In this directory there will be made two directories:

1. DYNAMO-HIA: this will contain the DYNAMO datasets and the excel macros.
2. DYNAMO-HIA-2.08 application

Startup

To open the DYNAMO-HIA prototype:

- Before you start DYNAMO-HIA, check that the tutorial data is on your computer. This is located in the directory to which you unzipped the DYNAMO-HIA-2.zip, under DYNAMO-HIA\DYNAMO-HIA database\Tutorial_Data.

- To start the software you should locate and run DYNAMO-HIA.exe, which will be in the directory DYNAMO-HIA-2.08 application\eclipse.
 - After starting the program, a file browser appears with the sentence “In the DYNAMO-HIA home directory data and simulations are stored”.¹ This window allows you to choose the working directory with the data you want to work with during this session. The working directory has to adhere to a fixed structure, i.e. containing certain directories. For the purpose of this tutorial browse folder “Tutorial_Data” you just copied on to your computer. If you decide to make a new directory, choose the desired location and type the desired name in the white open space “Folder”, DYNAMO will then create a working directory that follows the required structure. You can choose the working directory during a running session by going to the “File” menu.
1. After choosing an existing or creating a new working directory, the user interface appears (see Figure 1). The user interface allows to open and edit the data files that are stored in this directory, add new files to them, and setup and run simulations. The structure of the home directory (in this case: “Tutorial_Data”) mimics the directory structure of the folder specified as the home directory. The home directory always has a *Reference_Data* and a *Simulations* directory.

¹ Sometimes the message “Error starting Java VM” appears. This usually means the programs asks for more memory than is available on the computer. See “running DYNAMO-exe” (page 106) on how to low the amount of memory required.

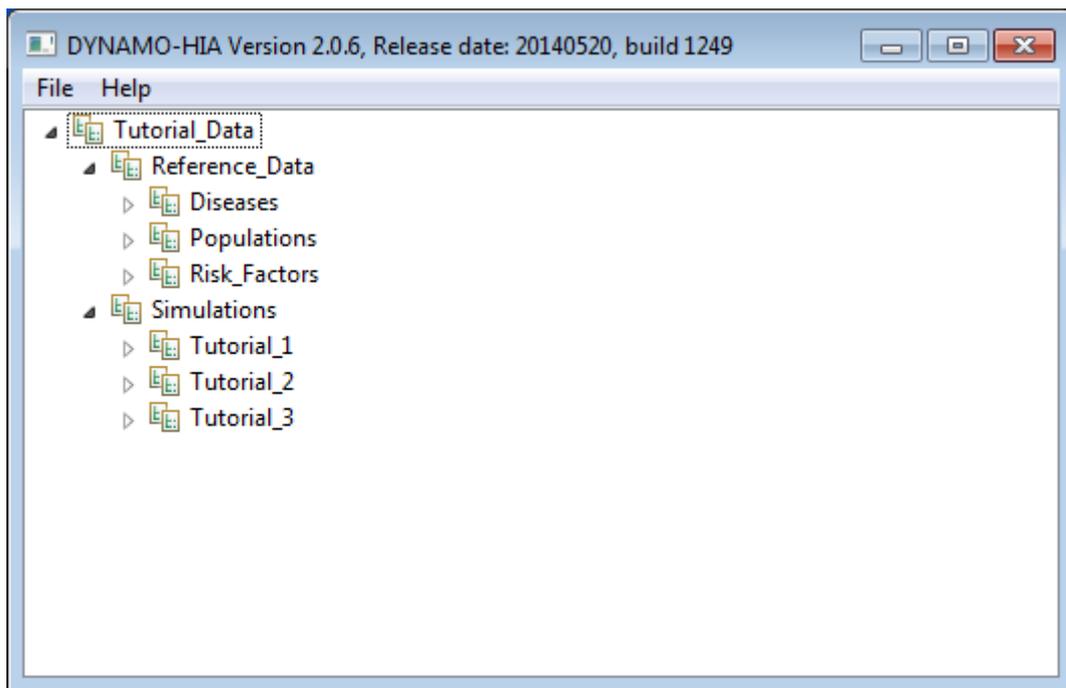


Figure 1: Starting Screen of User Interface (detail, text might vary)

Running your first Simulation

The user interface is split into two main directories. In the directory *Reference_Data* all the input data required to run simulations is stored. These are files consisting of data about the population, diseases, and risk factors. The example directory “*Tutorial_Data*” already contains all the data needed to run a simulation. But before proceeding you can explore the *Reference_Data* directory a bit. By pressing the + sign you can expand a directory and view the content. For example, when pressing the + sign next to the directory *Diseases*, all the disease that are available for simulation in this particular working directory are listed.

Click now the + sign right next to the *Simulations* directory to expand the view. A number of sub-directories are shown. Locate the directory *Tutorial_1* and click the + sign to expand the directory. Within the *Tutorial_1* directory, a single file is shown: *configuration*. Right click on this file and choose “*Configure and Run Simulation*” from the context menu. The *simulation screen* appears. In this screen all the technical choices for running simulations can be made.

Simulation

Name: Tutorial_1

Population: Batavia

Newborns: Yes No

Starting year: 2010

Minimum age: 0

Calculation time step: 1

Reference scenario name: Reference Scenario

Simulated population size: 10

Number of years: 25

Maximum age: 95

Random seed: 1

Scenarios

Scenario1

Name: Scenario1 % of Population Reached: 100

Target of Intervention

Min. Age: 0 Max. Age: 95 Gender: Male and Female

Change with respect to baseline simulation

Risk Factor Prevalence: UK_RF_BMI_cat3_Prev

Transition: UK_RF_BMI_cat3_TransitionsNetto

create delete

Save and Run

Import Save Save and close Close

Help

This is the central screen to specify the simulation that will be run. A simulation consists of one risk factor, one population, and one or more diseases. One or more scenarios can be specified (e.g. varying starting prevalence, target age of intervention, success rate etc.). No macro is provided for this configuration. For details click on the individual fields and consult the manual

Import an XML file with data. Such an XML file can be made with the special Excel spreadsheet that can be downloaded at www.dynamo-hia.eu

Figure 2: Pre-set simulation configuration screen for Tutorial_1

Configuring a simulation requires making several choices. For example, which disease to include, the length of a simulation, which risk factor to use, the specification of the intervention scenario and so on. Right now, no choices have to be made as in the *Tutorial_1* directory a finished simulation configuration is present. In this simulation we use BMI as a risk factor and compare how the population health of Batavia would develop if Batavia would have the risk factor prevalence of the UK. Batavia is a fictional country that shares almost all health and population characteristic of the Netherlands. This intervention affects all age groups and both sexes. We run the simulation for 25 years, include newborns, and made a number of further choices. For now, just click on the button “Save and Run”. Now DYNAMO-HIA runs the first simulation.

After a few second the *output screen* appears. The first image is always the “*Population Pyramid*”, that shows the overall population development over time and presents the share of the population that has a given diseases graphically. The share of the population that has a disease is colored in light red. In Figure 3, the light red area shows the share of the population that has at least one disease, i.e. the total disease burden. Now click on the “*autoRun*” button in the bottom left corner. This starts an animation that shows the development of population and population health for the projection time in one year increments. Note, however, that with larger simulations storing all data takes time. During this time the output screen is already shown, but does not yet react to clicking. So if nothing happens, be patient and try again a little later.

The population screen view has a number of options: One option is to see the disease burden for a particular disease. From the pull-down menu “diseases” another disease can be chosen. For example, when choosing “IHD” the light red area changes in shape and size, it now shows the prevalence of IHD in the population.

The pull-down menu “*scenario*” allows choosing different scenarios. In the case of *Tutorial_1* only two scenarios exist, the “reference scenario” and “Scenario 1”. When choosing “Scenario 1” an additional possibility is to click on the radio button in the middle of the screen and switch the y-axis from “*absolute value for scenario*” to “*difference with reference scenario*”. Activating this button changes the view of the population pyramid. Now the light red area shows the part of the population that has a given disease in both, the “reference scenario” and “Scenario 1”. The dark red area shows the part of the population that has the disease in “Scenario 1” but not in the

“reference scenario” (a yellow area would show the share of the population that has the disease in “reference scenario” but not in “Scenario 1”). The black area at the outer margin of the population pyramid shows the number of people that are alive in the in the “reference scenario” but not in “Scenario 1” (a grey area would show the share of the population that is alive in the “Scenario 1” but not in “reference scenario”). Also you can look more in detail by clicking and holding the left mouse button and then move to the right: a rectangle will appear that shows the area that will be shown in more detail at the moment that you release the mouse button. You can undo this by repeating the procedure, but moving to the left. Right clicking will show a menu, where you can choose to print or save the graph, or change the titles. Note, however, that any such changes to graphs will be temporary, and removed at the moment where you select another graph or tab.

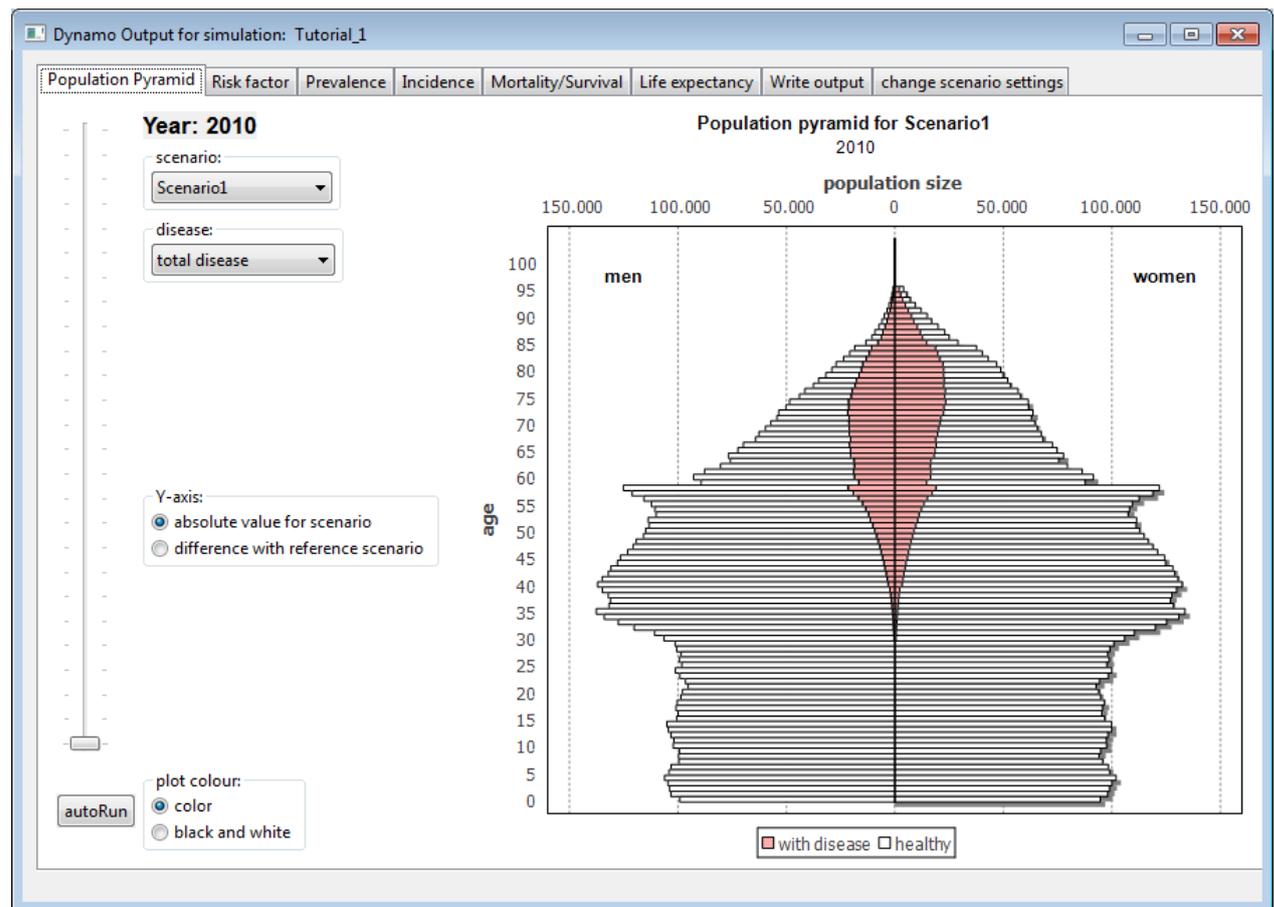


Figure 3: The population pyramid tab of the output screen

On the top of the output interface several different tabs are visible that allow analyzing the simulation results further. For example, the tab “life expectancy plots” shows the life expectancy for the different scenarios, their development over time, and the number of expected life years with a given disease. For a further exploration of the outcomes of “Tutorial_1” click on the tab “Prevalence”. This screen gives a graphical overview of the development of disease prevalence for the simulated scenarios. Again this screen allows several different choices. When first viewing the tab “Prevalence” after a simulation run, usually the plot graphs the development of the disease prevalence over time for all scenarios. In the case of “Tutorial_1” these are the “reference scenario” and “Scenario 1”. In the pull-down menu “disease”, another of the simulated diseases can be

chosen. When selecting the radio button “by gender”, the view changes and the plot shows the prevalence development separately for men, women, and total population. The scenario for which this is done can be selected in the pull-down menu “scenario”. Feel free to explore different options in the output screen.

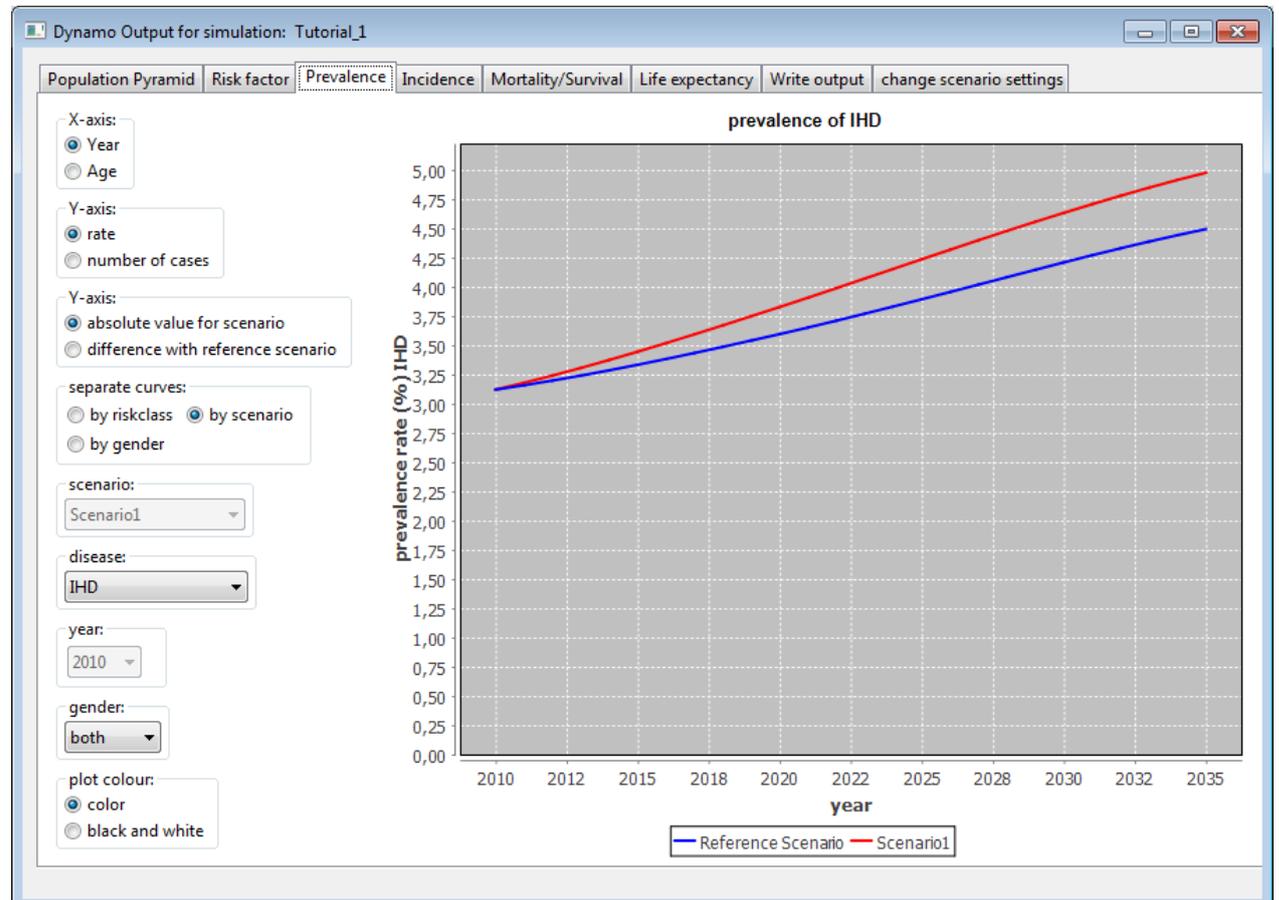


Figure 4: Disease Plots tab of the output screen (here development over time)

As a last step in this tutorial we want to draw your attention to the possibility of exporting the simulated output data. Click on the tab “Write output”. On this screen three different groups of decisions can be made. First, you can choose to export from a long list of file-types. The choice to be made here include a) format: “excel readable xml”, which – when given to MS excel - delivers the data in multiple tab workbooks and “csv” ; b) “per year of simulation” or “by cohort” and c) data on prevalence/incidence or

data on life expectancy. The second decision group option allows choosing to have the data “separate for man or women” or “total population”. The third option determines whether diseases are shown separately (“per disease”) or whether more detail on disease clusters (“per combination of disease”) is included in the output. When clicking on “write data”, you can choose a file name and file location where the raw output is saved.

The DYNAMO-HIA user interface

Reference Data

In the starting screen the directory “Reference_Data” stores all the data needed to run a simulation. DYNAMO comes with a set of data for a large number of EU populations (see the data manuals for details) and also allows to import own data either to augment the already existing data or to enter data for different populations. To assess the DYNAMO dataset for a particular country, you should set the working directory to this country. Under standard installation, the data can be found under “My Documents\DYNAMO-HIA\Country_data\CountryName”. For instance, for Spain this will be “My Documents\DYNAMO-HIA\Country_data\Spain”.

In this section we will explore the “Reference_Data” directory in more detail to give an overview of what kind of input data is needed. The data is usually – but not always – needed by age and sex. The age range is from 0 to 95 years of age. When percentages are needed as input, the range is between 0% and 100% (and not a fraction between 0 and 1).

In DYNAMO a directory can contain several sub-directories, which may have some further sub-directories and/or contain files. Within DYNAMO a file holds the actual data and can be recognized by not having a + sign right next to it. A file can be accessed by right-clicking on it and choosing “edit” from the context menu.

Expanding the directory “Reference_Data” by clicking on the + sign reveals three sub-directories:

- *Populations*
- *Diseases*
- *Risk_Factors*

Directory Populations

Expand the view of “*Populations*” by clicking on the + sign. This directory can contain several populations, if desired, but running a simulation requires only one fully specified population. In the tutorial, the population directory contains a single sub-directory named “*Batavia*”. This directory holds all the population data of the fictitious country of Batavia (which is surprisingly similar to the Netherlands for many health and population characteristics) needed to run a simulation. The files required to specify a population fully within DYNAMO are:

- *newborns*
- *overalldisability*
- *overallmortality*
- *size*

The file *newborns* contains the number of projected newborns for the given population. This is one of the few files in DYNAMO that does not require the data by sex, instead a sex ratio can be set. The sex ratio gives the number of boys born per girl. In European countries this ratio is usually close to 1.05.

The file *overalldisability* holds the average disability weight or percentage of disability in the general population. This is a number between 0 and 100, where 0 means

that no disabled persons are present in the population, and 100 means that the entire population is disabled. These data are used to calculate DALY-weighted or disability-free life expectancies, depending on whether one enters in this window (and other DALY-related windows) a DALY weight or a percentage of disability. The program does not make a distinction between the two, as the mathematical formulae for their calculation is identical. The data that are entered here determine which interpretation should be given to the output.

The file *overallmortality* holds the observed mortality rate for the population in question by age and sex.

The file *size* contains the population size of the population by age and sex. The age range is from 0 to 95.

Directory Risk Factors

The directory *Risk_Factors* contains all the data needed to specify a risk factor in DYNAMO. To run a simulation at least one risk factor has to be specified. The home directory “Tutorial” has already four different risk factors. Click on the + sign next to the directory “BMI-cat3”: a risk factor directory consist again of a number of sub-directories and contains in addition a file called *configuration*. The file *configuration* becomes important when creating a new risk factor and gives information on the meaning of the categories. In DYNAMO three different kinds of risk factors can be specified (categorical, compounding, and continuous). In this section we focus on categorical risk factors. The subdirectories of a specific risk factor in the directory *Risk_Factor* are:

- *Prevalences*
- *Relative_Risk_For_Death*

- *Odds-Ratios_For_Disability*
- *Transitions*
- *DurationDistributions* (only for compounding risk factors)

The directory *Prevalences* contains files with data about which share of the population is in which risk factor class (by age and sex). Here age refers to age at birthday for all prevalence data, while it refers to the age between this birthday and the next for all input related to transitions (like relative risks, incidences and mortalities). To run a simulation in which two situations with different prevalences are compared, at least two files need to be specified: one for the reference scenario and one for the intervention scenario. At least one file must be present to run a DYNAMO simulation.

What the risk factor prevalence looks like, depends on the type of risk factor:

For a categorical or compound risk factor, you have to enter (for each age and gender) the percentage in each exposure category (e.g. % normal weight, % overweight, % obesity) . For a continuous risk factor, you have to enter the mean value and standard deviation (SD) (e.g. mean BMI, SD BMI). For a compound risk factor, you also have to enter additionally information on duration (e.g. the % of former smoking that stopped 1, 2, ...20 year ago), under “DurationDistributions”.

The directory *Relative_Risk_For_Death* contains files with data about the relative risk of the risk factor on total mortality (age and sex specific). This file is optional and not required to run a simulation. If this file is used, the risk factor will influence the “other cause mortality”, that is mortality that is not mediated by the diseases that are included in the simulation.

The directory *Odds-ratios_For_Disability* contains a file with data on the odds ratios quantifying the association between the risk factor in question and disability. This file is not required to run a simulation.

The directory *Transitions* contains files with data on how people changes their risk factor status. The data consists of the age- and sex specific probability of switching from one risk factor category to another (say, from abstainer to light drinker). At least one file must be present to run a DYNAMO simulation.

The directory *DurationDistribution* only exists when the risk factor is a compounding risk factor (in contrast to a categorical or continuous). This directory contains a file with data about the duration of membership in a risk factor class (e.g. for former smoking the % that stopped 1, 2, ...20 year ago). This is used for risk factors where the relative risk is influenced by the duration of membership, such as former smokers, where the relative risk declines over time. This file has a standard name (durationPrevalence.xml) that cannot be changed.

Directory Diseases

The directory *Diseases* contains all the data needed to specify a disease that can be included in a simulation. Expanding the view shows a number of sub-directories, in the case of the working directory “Tutorial_Data” those are the already included diseases such as “Breast_Cancer” or “COPD”. Expand the view of a disease specific directory by clicking on the + sign right next to “Breast_Cancer”. This reveals a number of sub-directories that are the same for all diseases:

- *Disabiblity*
- *Excess_Mortalities*
- *Incidences*

- *Prevalences*
- *Relative_Risks_From_Diseases*
- *Relative_Risks_From_Risk_Factor*

These sub-directories contain files specifying the different aspects of the chronic diseases that can be simulated by DYNAMO. All are specified by age and sex. Here age refers to age at birthday for all prevalence data, while it refers to the age between this birthday and the next for all input related to transitions (like relative risks, incidences and mortalities). To include a disease in a simulation run, each of the disease sub-directories needs to contain at least one file with the necessary data (with the exception of the directory *Relative_Risks_From_Diseases* where adding data is optional as it is only applicable for some diseases). More files can be added; allowing running simulations with alternative specifications for a given disease. But in a single simulation run only one file of each sub-directory can be selected for an included disease.

The directory *Incidences* contains at least one file with the number of cases per person-years for the disease in question (by age and sex).

The directory *Prevalence* contains at least one file with data on the age- and sex specific prevalence of the population in percent (thus a number between 0 and 100).

The directory *Disability* contains at least one file with either the DALY weight of the respective disease in percent by age and sex, or the disabling impact of the disease. The user can estimate the disabling impact from individual survey data using the attribution tool. This tool provides age-specific disability hazards for each disease. The user has first transform these hazards into $1 - \text{EXP}(-\text{disease hazard})$. DYNAMO-2 internally uses “ $\text{EXP}(-\text{disease hazard})$ ”, or abilities. Even in the case where this information is not known or not intended to be simulated the directory still needs to

contain a file. We advise using a file specifying disability of zero for all ages, i.e. no disability induced by this particular disease).

The directory *Relative_Risks_From_Diseases* may contain files specifying the relative risk of contracting the disease when having another disease (by age and sex). This other disease has to be already specified. A good example is the case of diabetes: having diabetes increases the risk of contracting a heart disease; hence the relative risk of contracting IHD when having diabetes can be specified.

The *Excess_Mortalities* directory contains a file that specifies the additional mortality when having the disease, i.e. the difference for a person with the disease in question compared with a person without the disease. This is sometimes also called case fatality rate. This can be specified either as a rate or as median survival time. In addition, for a disease either the percentage of the “Acutely Fatal” or the percentage of “Cured Fraction” can be specified. This specification, when desired, changes the behavior of the disease from a pure chronic disease to

- either a disease where some people die instantly when contracting the disease (“Acutely Fatal”), e.g. stroke or IHD where some people die instantly
- or a disease where a share of people is being cured (“Cured Fraction”), e.g. some cancers.

Only one of these options can be chosen, and files containing non-zeros for both options will prompt the program to ask you to choose one of them, after which the other will be made zero.

The directory *Relative_Risks_From_Risk_Factor* contains the files that hold the information of how the underlying risk factor affects the risk of contracting the given disease. The files differ slightly by the type of risk factor. For example, for the risk

factor alcohol which has 5 categories, the file contains for each category the relative risk of obtaining the disease in this directory (by age and sex). In the case of a duration dependent risk factor (compound risk factor), the files differs slightly as one needs to enter more information for the category in which the relative risk depends on the duration in this class. In the case of smoking, for example, the risk of contracting a disease usually decreases for a former smoker over time. In this category (the duration category, in the example former smokers) one needs to specify the relative risk at the moment of entering the category (RRbegin), the relative risk after being in the category for a very long time (RRend) and a coefficient that represents how fast the RR is changing from RRbegin towards RREnd (alpha). This alpha is defined so that the relative risk is halfway between RRbegin and RREnd after $\ln(2)/\alpha$ years.

In case of a continuous risk factor, only a single relative risk is needed for each age and sex combination: this relative risk is the relative risk of increasing the risk factor with 1 unit. So for instance for BMI, it is the relative risk when increasing BMI with 1 kg.m^{-2} .

Configuring Simulations

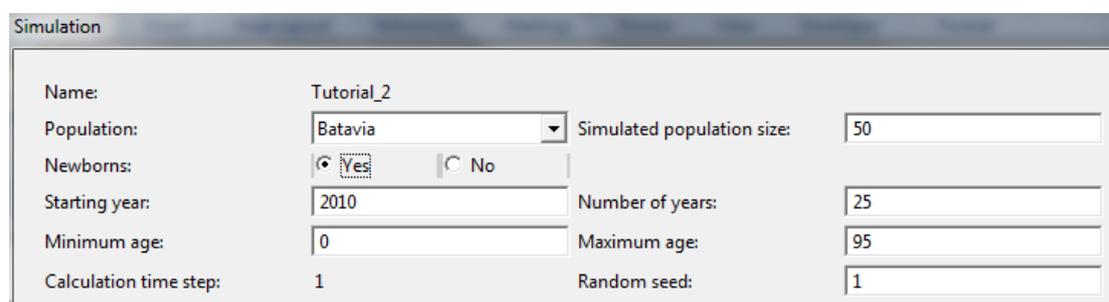
At the core of DYNAMO is the simulation of one (or more) scenarios where changes in the risk factor prevalence or the transition between risk factor states (or both simultaneously) are compared with a reference scenario. This allows quantifying what changes of population health materialize over time when a risk factor is altered. In this section we will talk in more detail about the simulation screen, outlining all possible options. The issue of choosing scenarios is addressed in more detail on page 68.

Expand the directory “*Simulations*” by clicking on the + sign and right click on the directory “*Tutorial_2*”. In the context menu choose “*Configure and run*”

simulation". A screen like in Figure 5 appears². This is the simulation configuration screen and a number of choices are required before running a simulation.

In the bottom half, four different tabs are visible:

- *Scenarios*
- *Risk Factor*
- *Diseases*
- *Relative Risks*



The screenshot shows a window titled "Simulation" with the following configuration options:

Name:	Tutorial_2		
Population:	Batavia	Simulated population size:	50
Newborns:	<input checked="" type="radio"/> Yes <input type="radio"/> No		
Starting year:	2010	Number of years:	25
Minimum age:	0	Maximum age:	95
Calculation time step:	1	Random seed:	1

Figure 5: Top half of the simulation configuration screen

On the top half, decisions about the population and some technical aspects of the simulation can be specified. These are:

Name: Shows the name of the simulation run which is taken from the name of the directory and cannot be changed in the simulation screen views. (*It should read "Tutorial_2"*)

² In order to open the simulation screen, the program needs the presence of one valid risk factor and one valid disease in the reference_data directory. Valid disease means that at least one prevalence, incidence, excess mortality and disability file need to be present; Valid risk factor means that at least one prevalence and one transition file needs to be present.

Simulated Population: This is a pull-down menu where the population to be simulated can be selected. When only one population is defined in the directory *Population*, this population appears as the default. *(In Tutorial_2 it should read “Batavia”)*

Reference scenario name: This is a field where you can enter the name of the reference scenario (the business as usual scenario).

Population size: For the risk factor behavior, DYNAMO uses a micro simulation. A number of individuals are simulated and are a representative sample of the whole population. The number entered here is the number simulated for each age/gender combination. A large number usually yields a lower stochastic variation in the risk factor histories. The upper practical limit depends on a number of factors (such as computer memory and complexity of scenario). *(Enter here a 50 for the purpose of the tutorial. This implies that 50 times 95 ((the number of age classes) times 2 (males and females) = approx. 10,000 persons are simulated.)*

For scenarios with zero-transition rates and categorical risk factors, no stochastic variation is present, so this number can be kept small.

Newborns: Whether or not newborns are included in the simulation. This is only possible when the minimum age is set to zero (as otherwise one would simulate a population with a strange gap between newborns entering the simulation, and the starting age of the simulated population. *(Include newborns by clicking on “yes”)*

Starting year: The year the simulation starts from. The current calendar year is the default for a new simulation. When newborns are used, the data should provide newborns for all years after this starting year. *(It should read the current year).*

Number of years: The number of years DYNAMO projects the scenarios in the future. *(Use 25 for this tutorial)*

Minimum age: Minimum age of the population you want to simulate. *(Choose “0”)*

Maximum age: Maximum age of the population you want to simulate. The maximum value in the initial population of the DYNAMO model is 95 although the model simulates internally to higher ages. *(Choose “95”)*

Random seed: The value used to initialize the random number generator used during the simulation. Any number will do, but when running two different simulations with exactly the same data, choosing the same random number ensures identical results. Otherwise, random variation alters the simulation outcomes slightly. *(Use “1”).*



The image shows a screenshot of the 'Risk Factor' tab in a simulation configuration interface. The interface has a tabbed header with 'Risk Factor', 'Diseases', 'Relative Risks', and 'Scenarios'. The 'Risk Factor' tab is active. Below the header, there are three rows of configuration options, each with a label on the left and a dropdown menu on the right:

- Risk Factor:** The dropdown menu is set to 'BMI'.
- Risk Factor Prevalence:** The dropdown menu is set to 'NL_RF_BMI_cat3_Prev'.
- Transition:** The dropdown menu is set to 'NL_RF_BMI_cat3_Transition_Netto'.

Figure 6: Risk Factor tab of simulation configuration screen (detail)

Risk Factor Tab

Click on the Risk Factor tab. This tab consists of three pull-down menus. The first on the top, “Risk Factor”, allows choosing the directory that contains the desired risk factor. The other two menus allow choosing the file with data on the risk factor prevalence and the file with the transition probabilities between risk factor states. If only one file exist for the chosen risk factor, this file is the default.

The risk factor prevalence chosen here represents the risk factor exposure in the baseline year in the business-as-usual (reference) scenario.

As DYNAMO is a dynamic tool, in addition the user should specify whether, and if so, how this exposure will change in the future. In other words, what transitions between risk factor categories are persons expected to make in the future. DYNAMO assumes that these transitions remain valid over the entire projection period (25 years in this tutorial).

In DYNAMO there are three options to specify the future transitions:

1. User-specified transitions: the user provides data on transitions between the risk factors categories (e.g. smoking start probabilities and quit probabilities rates, or on trend for continuous exposure (e.g. increase in mean BMI of 0.02 for each age year).
2. Net-transitions: The user assumes that the age-specific prevalence of exposure in the population will remain the same (thus prevalence by age and sex does not change). This approach is very similar to the use of period life expectancy, where for a newborn the currently observed age-specific mortality pattern is assumed to remain valid. This approach ignores any cohort effects. This approach is named

“net transitions” in DYNAMO-HIA, because DYNAMO derives the minimum transitions that are needed to keep the age-specific prevalence unchanged in the future. DYNAMO can only calculate nett-transitions for the reference scenario. In the case nett transitions are also specified for alternative scenarios, DYNAMO uses the nett transition rates calculated from the prevalence of the reference scenario also for the alternative scenario. In other words, it assumes that the future dynamics of the risk factor remain the same. In order to use nett-transitions based on the prevalence of an alternative scenario, a trick can be used, which is described in the box on page 65.

3. Zero-transitions: Persons are assumed keep the exposure in the baseline year throughout their life until they die. Hence, persons having a normal weight at baseline keep that during the entire period or until they die. This approach is named “zero transitions” in DYNAMO, as there are no transition between risk factor categories or changes in mean BMI in the future when persons age.

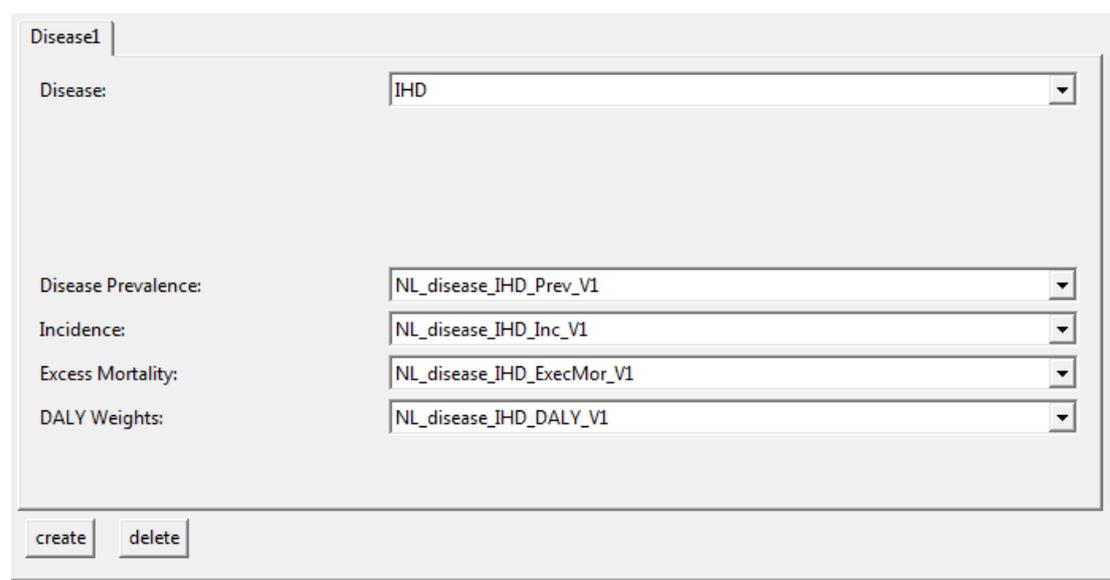
(Choose “BMI” as the risk factor. For the risk factor prevalence choose the file “NL_RF_BMI_cat3_Prev”. For transitions choose the file “NL_RF_BMI_cat3_Transitino_Netto”.)

Diseases Tab

Click on the *Diseases* Tab. This tab allows choosing which diseases to include and further specifies them, when desired. Click on the button “*create*” and a view like in Figure 7 appears. At the top is a pull-down menu, showing the disease that can be included in the simulation. (The names in this pull-down menu are the directory names

in the “Disease” directory of the “Reference_Data”). For every disease, four files can be specified. The prevalence of the disease (“Disease Prevalence”), the incidence of the disease (“Incidence”), the excess mortality (“Excess Mortality”), and the DALY weights (“DALY Weights”). The pull-down menus shows all the files contained in the respective sub-directory of the chosen disease. This allows, when desired to try out alternative specifications of the same disease in different simulations runs. If only one file exist in each sub-directory, this file is the default.

(Click nine times on the “create” button. In our tutorial data set, each of the nine included diseases has exactly one file for prevalence, incidence, mortality, and disability (in this case DALY weights). Hence, the default choices are the right files for the simulation run in Tutorial_2.)



The screenshot shows a window titled "Disease1" with a tabbed interface. The "Disease:" dropdown menu is set to "IHD". Below it, four dropdown menus are listed for "Disease Prevalence:", "Incidence:", "Excess Mortality:", and "DALY Weights:", each with a default file path: "NL_disease_IHD_Prev_V1", "NL_disease_IHD_Inc_V1", "NL_disease_IHD_ExecMor_V1", and "NL_disease_IHD_DALY_V1" respectively. At the bottom of the window are two buttons: "create" and "delete".

Figure 7: Specifying a disease in the simulation configuration screen (detail)³.

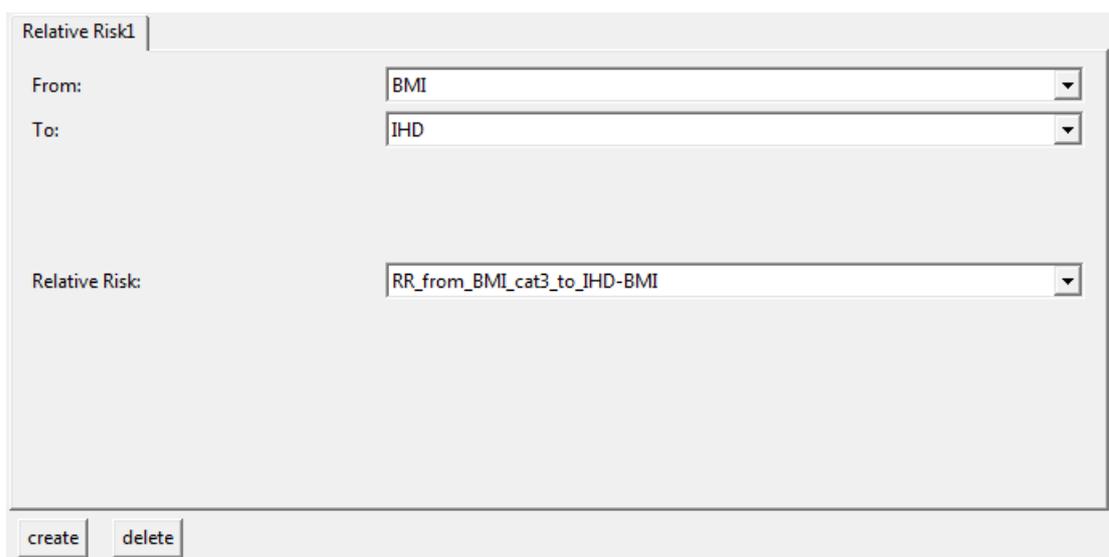
Relative Risk Tab

³ New printscreen will be added with new terminology

Select the Relative Risk tab. This tab allows determining which relative risks or odds ratios (in case of disability) to include. Click on the button “create” and a view like in Figure 8 appears. The view consists of three pull-down menus. The first on the top, “From”, allows choosing the risk factor. This pull-down menu can have several options. The first option is always the risk factor chosen in the “Risk Factor” Tab. When in the reference data, one (or more) relative risk from a disease has been included, then these diseases can be chosen as risk factors as well. This means several relative risks / odds ratios can be specified: one from the risk factor to every included disease, from the risk factor to death, from the risk factor to disability and from one (or more) included disease to one (or more) included disease. The disease is chosen in the pull-down menu “To”. When the risk factor and the disease (or death) are specified, then the pull-down menu “Relative Risk” allows choosing a file that contains the actual data. When only one file has been specified for a given “Risk-Factor-to-Disease-Relationship”, this file is the default selection.

In this tab it is possible to select relative risks that refer to diseases that are not (yet) selected on the disease tab. If a simulation is run with a relative risk for a disease that is not included on the disease tab, this relative risk is ignored in the simulation.

(Press the “create” button 12 times. This specifies the relative risk from BMI to the nine included diseases, from BMI to death, and the relative risks from diabetes to stroke and IHD, respectively. As we have only one relative risk file for each of these “From”-“To”-combinations the default choices are the right files for the simulation to be run in Tutorial_2.)



Relative Risk

From: BMI

To: IHD

Relative Risk: RR_from_BMI_cat3_to_IHD-BMI

create delete

Figure 8: Specifying a relative risk in the simulation configuration screen (detail).

Scenario Tab

Click on the Scenario tab: This tab allows configuring the (alternative) scenarios which are being simulated. In effect, by having specified the risk factor (prevalence and transition), the included diseases, and the relative risks, the reference scenario is fully specified. In the Scenario Tab one or more alternative scenarios can be specified by making several, alternative choices. Click on the button “create” and view like in Figure 9 appears. The main choices are in the pull down menu “Transitions” and “Risk Factor Prevalence”, where the alternative scenarios can be specified. The pull-down menus allow choosing from the files which are in the directory of the chosen risk factor. See the description under “risk factor tab” for a general description of these choices.

To specify what is expected in risk factor exposure due to the policy or intervention (=intervention scenario), the user can change the following as compared to the reference scenario:

1. Change the baseline exposure

2. Change the future transitions
3. Change both baseline exposure and transition.

If the user wants to change only one (1 or 2), he has to choose the other input equal as that in the reference scenario (= as selected on the risk factor tab).

It is important to realize that if, for instance, the user only changes baseline exposure and keeps the transition rates unchanged, due to dynamic behavior, in the long run other prevalence rates are realized. For instance, they may return to the baseline prevalence rates (of the reference scenario) if the latter reflect the steady-state situation of the transition rates. An exception is when nett transitions are used: With nett transitions rate the age-specific prevalence rates are kept constant as good as possible. Therefore they do not exhibit this type of dynamic behavior. (see Kasstele, J., et al. (2012). "Estimating net transition probabilities from cross-sectional data with application to risk factors in chronic disease modeling." *Stat Med* 31(6): 533-543.)

Changing only the transition rates assumes that the intervention changes future behavior. DYNAMO assumes this new behavior to remain during the entire simulation period.

In a scenario you must chose either a different transition dataset or a different risk factor prevalence dataset from that chosen on the risk factor tab. Therefore, if the risk factor prevalence is the same as that on the risk factor tab, the transition dataset from the risk factor tab will not be visible, and visa versa. It can occur that the list of choices is not refreshed correctly after changing the other choice. In that case the dataset does not reappear in the list after changing the other choice. Clicking on the risk factor tab and back to the scenario tab will solve this.

Furthermore, success rate and target of intervention can be specified. The success rate is between 0 and 100% and the target of the intervention can be specified for a desired age range (from 0 to 95) and gender (male, female, or both). This setting determines to which extent the alternative transitions and risk factor prevalence affect the simulation. This setting, however, can be changed in the output screen, i.e. after the simulation has been run, see the section on Change scenario settings.

Scenario1

Name: Scenario1 % of Population Reached: 100

Target of Intervention

Min. Age: 0 Max. Age: 95 Gender: Male and Female

Change with respect to baseline simulation

Risk Factor Prevalence: UK_RF_BMI_cat3_Prev

Transition: UK_RF_BMI_cat3_TransitionsNetto

create delete

Figure 9: Specifying a scenario in the simulation configuration screen (detail).

Starting the simulation

By pressing the “Save and Run” button, the simulation starts running. Depending on the complexity of the configuration (e.g. chosen population size, number of diseases etc.) the running time may vary. The program does not respond when running but shows the output screen as soon as it is finished. During simulation progress bars appear that indicate the progress. Clicking on a screen during simulation will stop the updating of the progress bar. The simulation, however, will continue, and results will appear in due time.

Output Screen in more Detail

After running the simulation, an output screen appears. This screen gives an overview (graphically and numerically) about the simulated scenarios. In addition, this screen allows exporting the results as raw data for further analysis in another software (such as MS Excel).

In the directory “Simulations” expand the sub-directory “Tutorial_3” by clicking on the + sign. “Tutorial_3” already contains a run simulation that created three sub-directories. The file “configuration” contains all the detailed specification of the simulation run. Click on the + sign next to the directory “results”. This directory holds as content the file “resultsObject.obj”, which stores and allows accessing the simulation output without running a simulation again. Right click on the “resultsObject.obj” and choose “View results” from the context menu (see Figure 10). After a few moments the output screen appears. The output screen has a number of different views that can be accessed via tabs. Those tabs are:

- Population Pyramid
- Prevalence (also may include disability)
- Incidence
- Risk factor
- Life expectancy
- Mortality/Survival
- Write output
- Change scenario settings

All plots shown in the output screen share some common technical features: by clicking on a point on the plot and moving the mouse to the right, an area can be selected to be zoomed in. This step can be repeated as desired. By clicking on a graph

and moving the mouse to the left, the standard zoom is restored. Right clicking on a graph opens a context menu with a number of technical options. Most notably, the option “Save as...” allows saving the graph as a separate file for later inclusion in MS Word. But other options also include changing the labels, font type, letter size and so on.

The simulation run in “Tutorial_3” is similar to “Tutorial_1” and “Tutorial_2”. The population is taken from Batavia (a fictitious country very similar to the Netherlands), the risk factor is BMI in three categories (normal, overweight, obese), and the simulation includes nine diseases. The “reference scenario” has the Batavian risk factor prevalence and transition probabilities that keep this risk factor prevalence constant. The intervention scenario, called “UK_Prevalence”, changes the BMI risk factor prevalence of Batavia to the one of the UK - which has a higher share of overweight and obese – and transition probabilities that keep the UK prevalence constant.

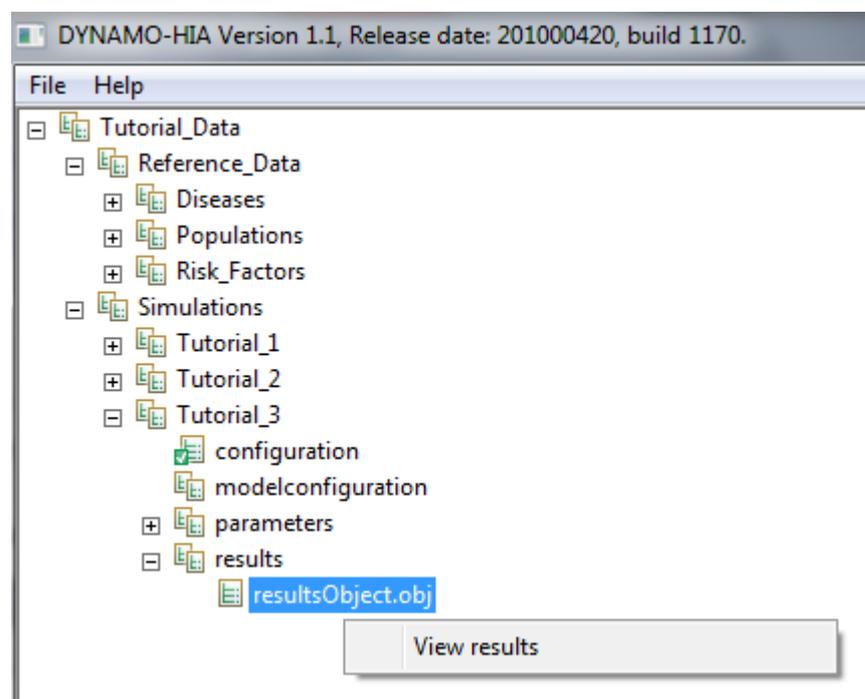


Figure 10: View of the “resultsObject.obj” in the user interface (detail)

Population Pyramid

The population pyramid screen gives a graphical overview of the total population, coloring the share of the population that is diseased, shows the development over time, and allows comparison between scenarios. This screen has several options that allow altering the plot and analyze different aspect of the data.

Click on the “*autoRun*” button in the bottom left corner. This starts an animation that shows the development of population and population health for the projection time in one year increments. A particular year can be chosen by moving the slider or clicking on the appropriate tick at the left hand ruler.

At the top of the screen, the pull-down menu (“scenario”) allows choosing the scenario for which the graph is plotted. The pull-down menu below (“diseases”) allows choosing which of the simulated diseases are shown. The user can also select “disability”. With the further options all persons that are diseased (“total diseases”) or have a disability (“disability”) can be shown. The graph is color coded: the light red area shows all persons that have the selected diseases, or have disability and the white area are the people that are healthy. Now chose scenario1 under “scenario”, and then click under “Y-axis” on “difference with reference scenario”. Now more colours appear. The light red area now shows the part of the population that has a given disease in both scenarios, the “reference scenario” and “UK_Prevalence”. The dark red area shows the part of the population that has the disease in “UK_Prevalence” but not in the “reference scenario” (a yellow area would show the share of the population that has the disease in “reference scenario” but not in “UK_Prevalence”). The black area at the outer margin of the population pyramid shows the number of people that are alive in the “reference scenario” but not in “UK_Prevalence” (a grey area would show the share of the population that is alive in the “UK_Prevalence” but not in the “reference scenario”).

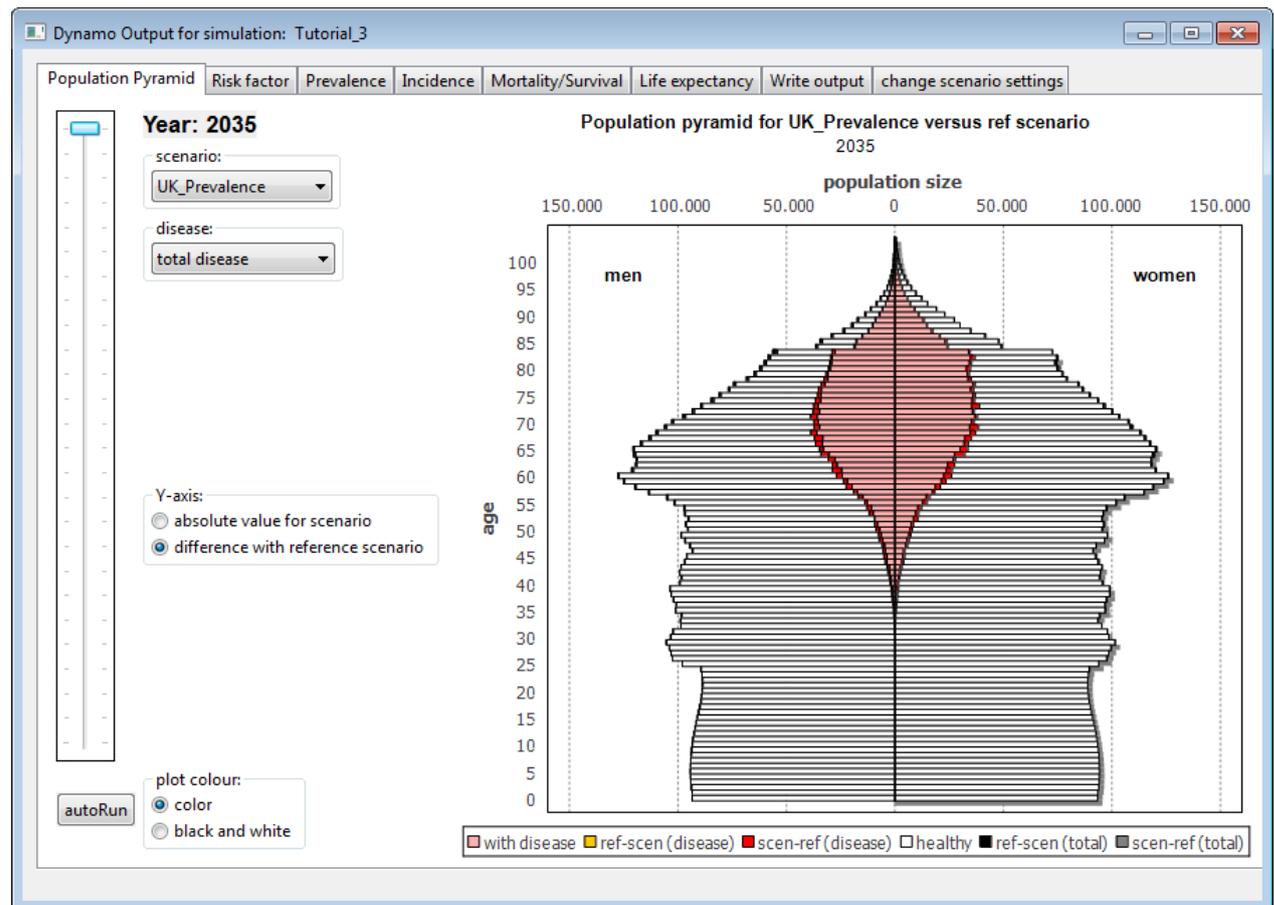


Figure 11: Population Pyramid Screen

Prevalence plots

The tab “Prevalence” graphs the disease prevalence or disability prevalence. A number of options can be changed and combined to graph and analyze different aspects of the data. However, not all combinations are possible. In those cases the affected menus are made in- accessible (by graying them out).

The menu “X-Axis” has two radio buttons: either “Year” or “Age”. When “Year” is selected, the development of disease prevalence over time is shown. When switching to “Age”, then the age specific prevalence is shown. In this case, the pull down menu “year” becomes available and the desired simulation year can be chosen for which the age- specific prevalence is shown.

The menu “Y-axis” exists twice. The top “Y-axis” menu has two radio buttons: either “rate” or “number of cases”. When “rate” is chosen, the prevalence is given in percentage of the total population. When “number of cases” is chosen the absolute number of cases is plotted. Right below the “Y-axis” menu has two radio buttons as well. Here the choices are “absolute value for scenario” or “difference with reference scenario”. When “difference with reference scenario” is chosen, the plot calculates and plots the difference between the selected intervention scenario (in the case of “Tutorial_3” this is “UK_Prevalence”) and the reference scenario. This difference is either the difference in percentage points (when “rate” is chosen) or absolute numbers (when “number of cases” is chosen).

The menu “separate curves” has three radio buttons: “by riskclass”, “by scenario”, or “by gender”. When selecting “by scenario”, the curves compares the prevalence of a given disease for the included scenarios. When selecting “by riskclass” the curves are drawn for each risk factor class of the simulated risk factor for one scenario (The desired scenario can be chosen from the pull down menu “scenario”). For interpretation of these graphs also see page 85. The choice “by gender” shows the prevalence for males, females and both for one scenario (The desired scenario can be chosen from the pull down menu “scenario”).

The pull down menu “diseases” allows choosing the disease to be plotted.

The pull down menu “gender” allows choosing for which gender (male, female, or both), when applicable.

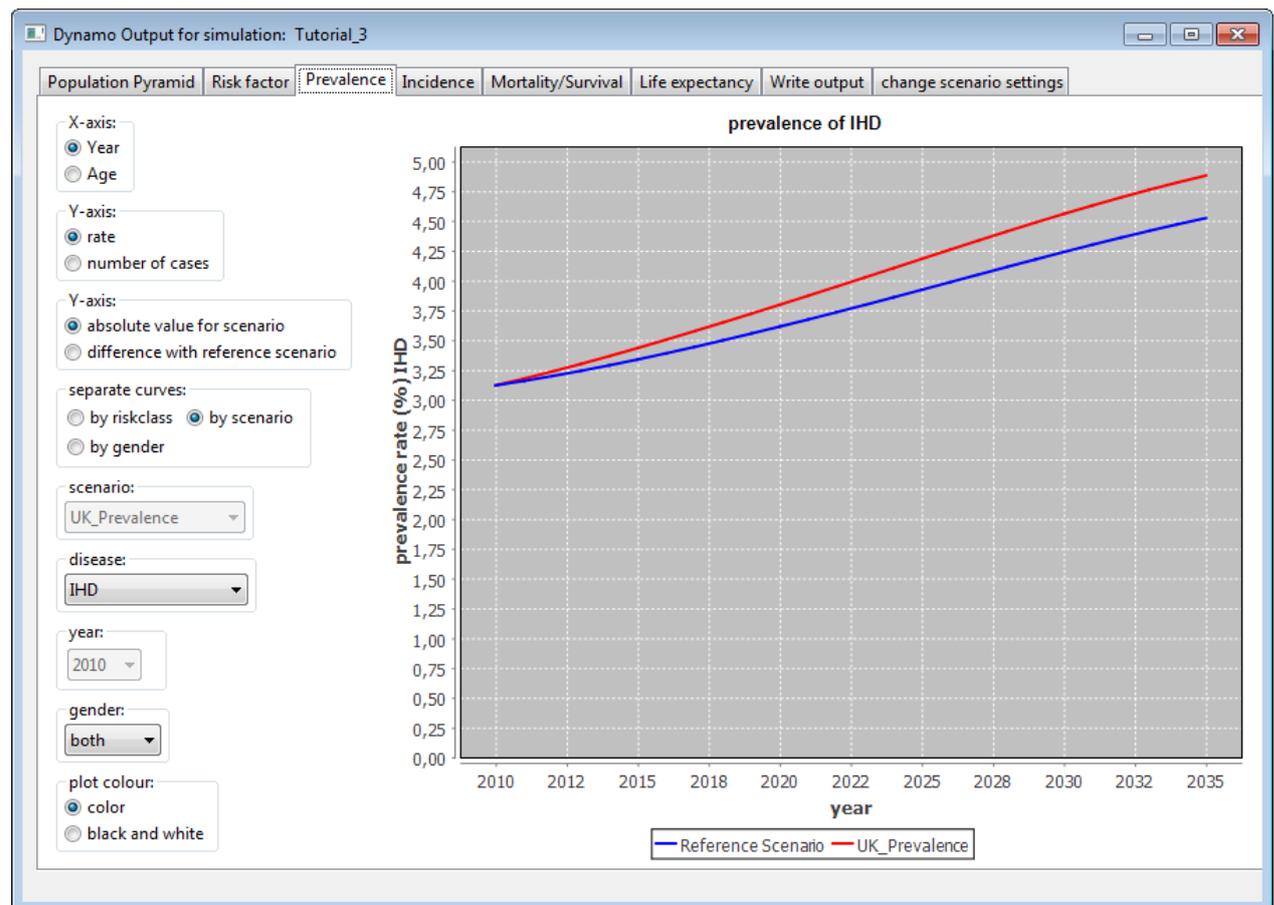


Figure 12: Prevalence plot screen

Incidence plots

The tab “Incidence” graphs the one-year (cumulative) disease incidence. A number of options can be changed and combined to graph and analyze different aspects of the data. However, not all combinations are possible. In those cases the affected menus are made in- accessible (by graying them out). The options are the same as those for the prevalence plots, so we refer to the previous paragraph for an explanation.

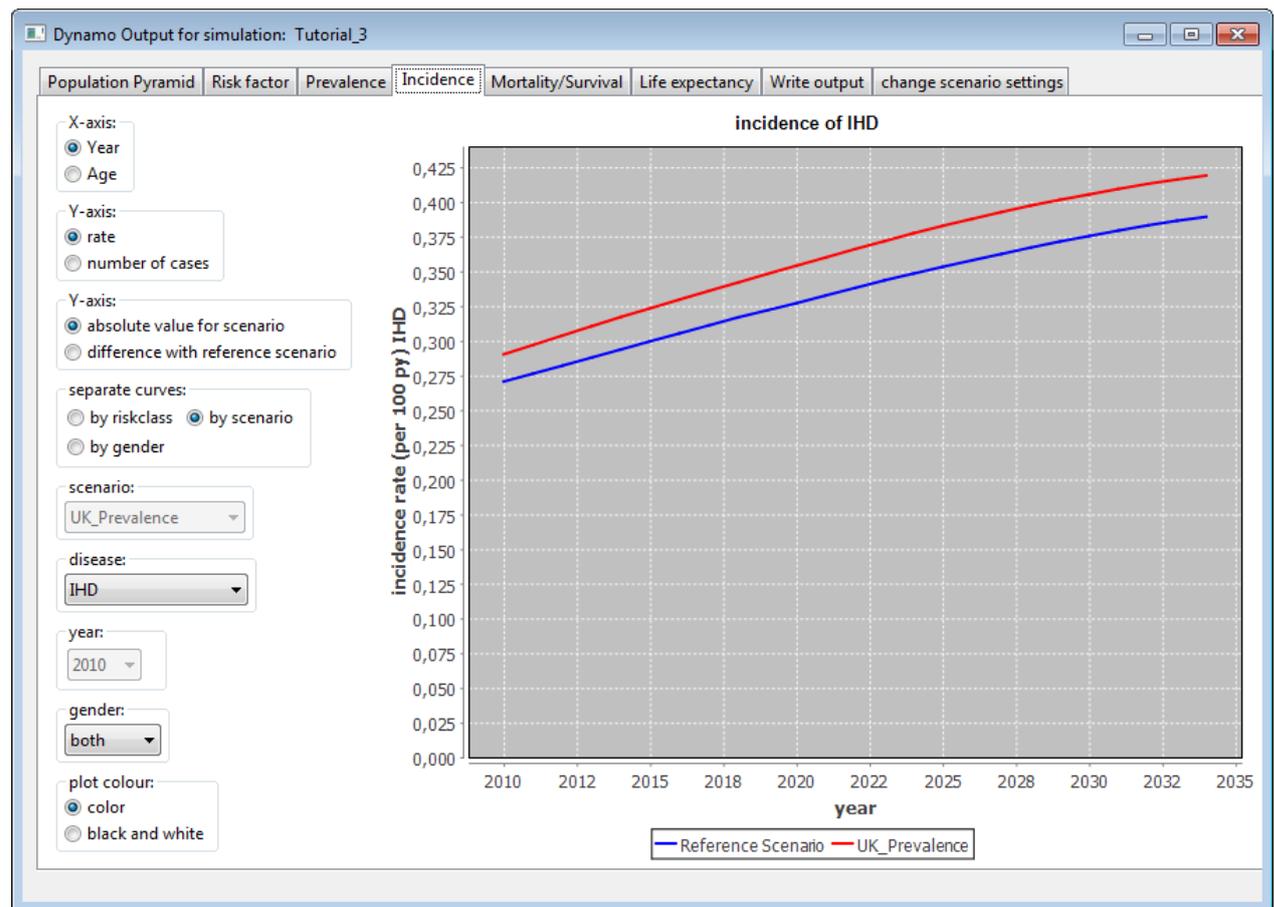


Figure 13: Incidence plot screen

NOTE: The incidence display here is the cumulative incidence in one year in the entire population. This means that the nominator of the incidence are the number of cases that get the disease during the simulated year (including those that die shortly after). The denominator is the entire population at the start of the simulated year, including persons that already have the disease. In contrast, the incidence rate that is input for the program, is the incidence rate as is usually determined by epidemiological studies, which is the instantaneous transition rate to disease in those without the disease. In that case the denominator consists only of disease-free individuals. This means that the output incidence will usually be smaller than the input incidence rate.

Risk factor plots

The tab “Risk factor” graphs and compares the risk factor prevalence for all scenarios by risk factor class. A number of options can be changed and combined to graph and analyze different aspects of the data. However, not all combinations are possible. In those cases the affected menus are made in-accessible (by graying them out).

The menu “X-Axis” has two radio buttons: either “Year” or “Age”. When “Year” is selected, the development of risk factor prevalence over time is shown. When switching to “Age”, then the age specific prevalence is shown. In this case, the pull down menu “year” becomes available and the desired simulation year can be chosen for which the age- specific prevalence should be plotted.

The menu “Y-axis” exists twice. The top “Y-axis” menu has two radio buttons: either “rate” or “number of cases”. When “rate” is chosen, the prevalence is given in percentage of the total population. When “number of cases” is chosen the absolute number of cases is plotted. The lower “Y-axis” menu has two radio buttons as well: Here the choices are “absolute value for scenario” or “difference with reference scenario”. When “difference with reference scenario” is chosen, the plot calculates and plots the difference between the selected intervention scenario (in the case of “Tutorial_3” this is “UK_Prevalence”) and the reference scenario. This difference is either the difference in percentage points (when “rate” is chosen) or absolute numbers (when “number of cases” is chosen).

The pull-down menu “risk class” allows choosing the desired risk factor class to be plotted. (In the case of “Tutorial_3” those are: Normal, Overweight, Obese).

The pull-down menu “gender” allows plotting the risk factor prevalence for one gender only (“men” or “women”) or both combined (“both”).

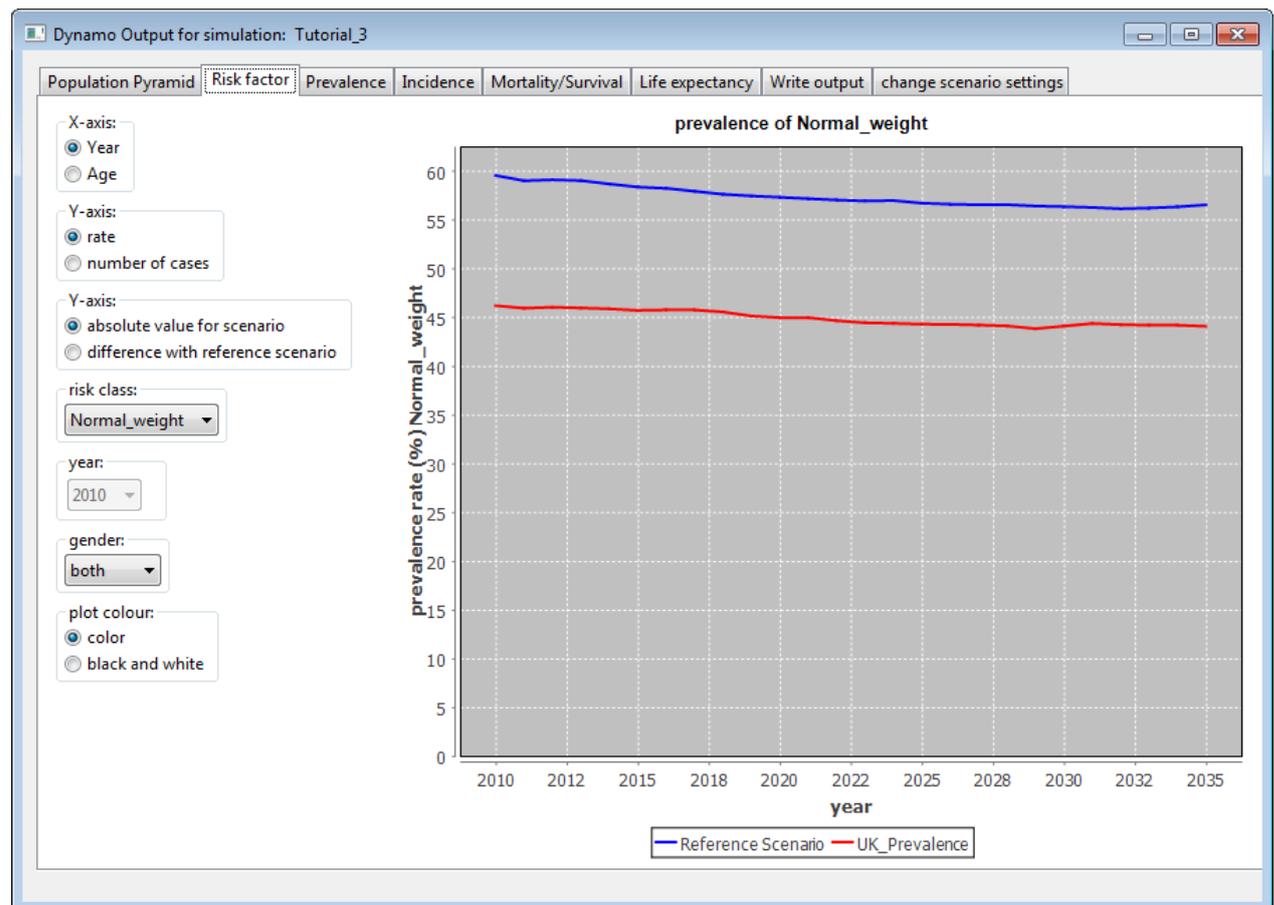
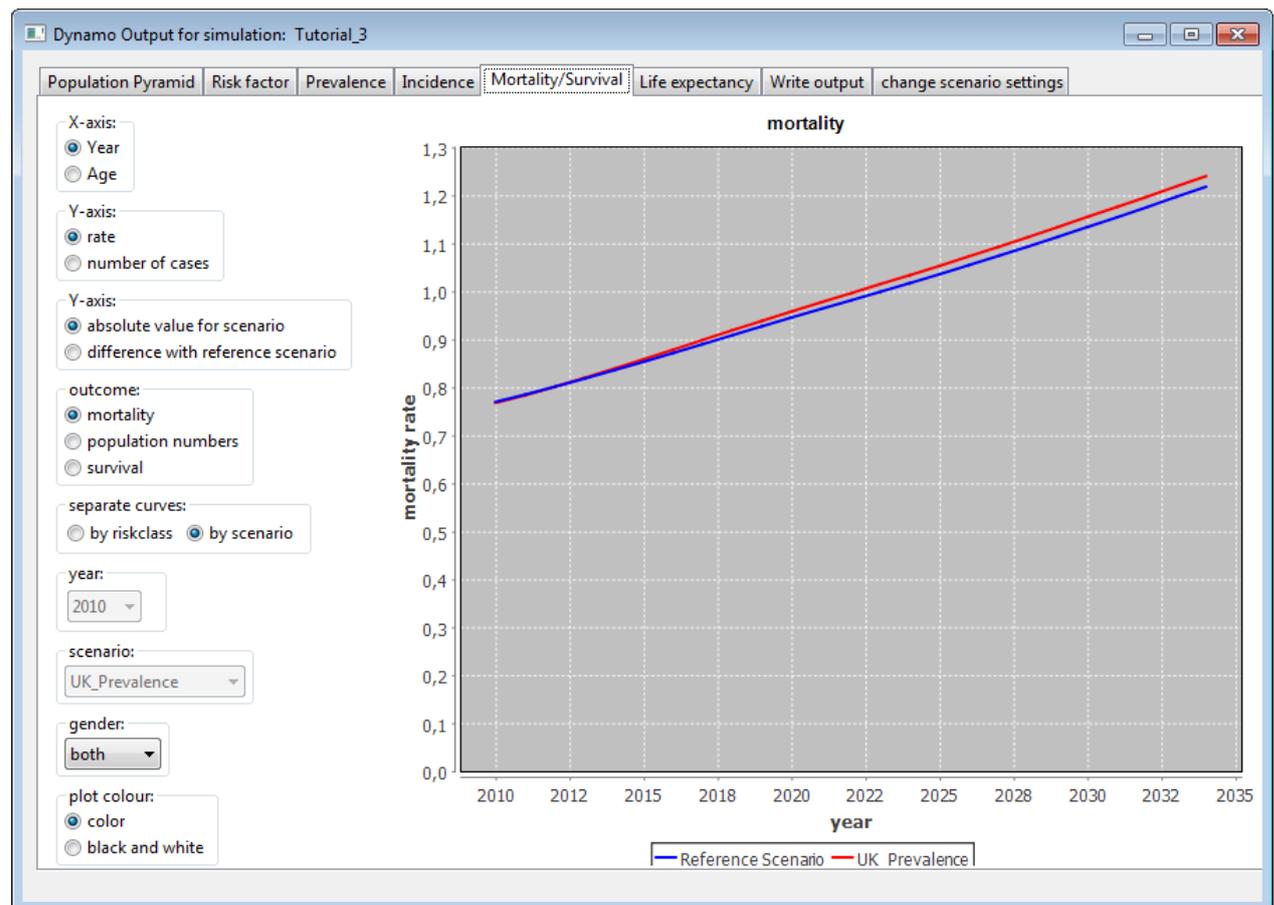


Figure 14: Riskfactor plot screen

Mortality/survival plots

The tab “Mortality/survival plots” graphs and compares the mortality, the population numbers or survival rates for all scenarios. A number of options can be changed and combined to graph and analyze different aspects of the data. However, not all combinations are possible. In those cases the affected menus are made in-accessible (by graying them out).



The menu “X-Axis” has two radio buttons: either “Year” or “Age”. When “Year” is selected, the development of the risk factor prevalence over time is shown. When switching to “Age”, then the age specific prevalence is shown. In this case, the pull down menu “year” becomes available and the desired simulation year can be chosen for which the age- specific prevalence is shown.

The menu “Y-axis” exists twice. The top “Y-axis” menu has two radio buttons: either “rate” or “number of cases”. When “rate” is chosen, the rate is given in percentage of the total population. When “number of cases” is chosen the absolute number of cases is plotted. The lower “Y-axis” menu has two radio buttons as well: Here the choices are “absolute value for scenario” or “difference with reference scenario”. When “difference with reference scenario” is chosen, the plot calculates and plots the difference between the selected intervention scenario (in the case of “Tutorial_3” this is “UK Prevalence”)

and the reference scenario. This difference is either the difference in percentage points (when “rate” is chosen) or absolute numbers (when “number of cases” is chosen).

The menu “outcome” has three radio buttons: “mortality”, “population numbers” or “survival”. When choosing “mortality” the mortality rate is shown, either in percentage when “rate” is selected or in absolute number of deaths when “number of cases” is selected. When “population numbers” is selected, the number of persons in the population is shown (no rate is possible). When “survival” is selected, the development of the initial population over time is shown, either in percentage when “rate” is selected (with the population of the starting year as base) or in absolute number of deaths when “number of cases” is selected.

The menu “separate curve” has two radio buttons: “by risk class” and “by scenarios”. When choosing “by risk class” the mortality or survival is shown separate for each risk class for one of the scenario’s. Which scenario is displayed can be chosen by the menu “scenario”. When choosing “by scenario” the mortality or survival is shown separately for each scenario.

Life expectancy plots

The “Life expectancy” tab graphs and compares the life expectancy between scenarios by gender. Several choices can be made to alter the plot. The pull-down menu “diseases” allows choosing one of the simulated diseases, “total disease”, “disability” or “none”. When choosing the option “none”, the bars reflect total life expectancy. When choosing a particular disease, the bars are split: the lighter color represents the expected life years without disease and darker colors represent the expected life years with the chosen disease.

The menu “type of life expectancy” has two radio buttons: “cohort” and “period (Sullivan Method)”. The cohort life expectancy calculates the life expectancy of a cohort that would be followed through time. The starting is the starting year of the simulation and the figure reflects the experience of a cohort observed until every member dies. The pull-down menu “age” allows choosing for which cohort this is done. The option “at age: at birth” shows the life expectancy for a cohort born in the starting year of the simulation and followed until everybody dies. The option “at age: 50” would follow the cohort that is 50 years old at the starting year of the simulation until everybody dies.

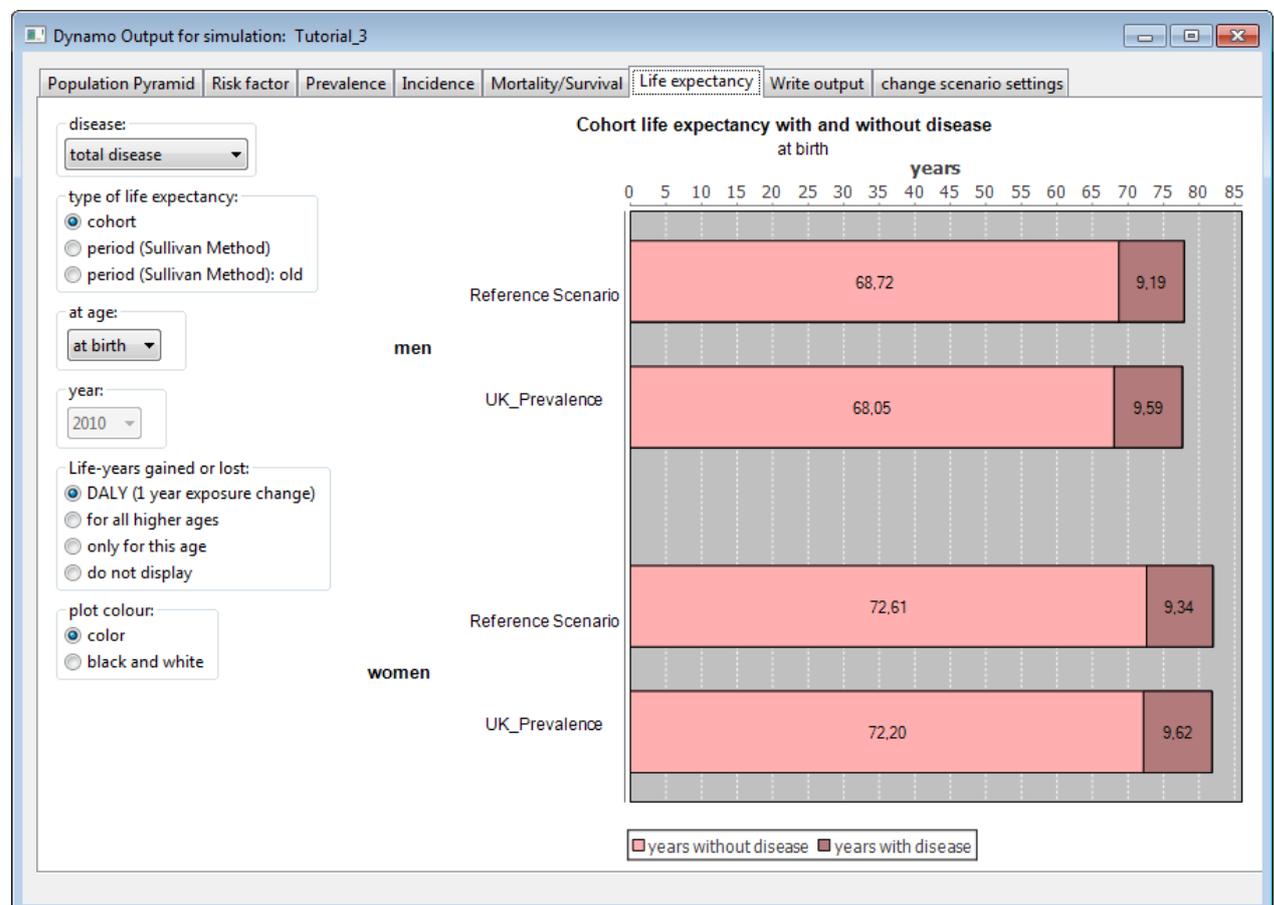


Figure 15; Life expectancy screen

The period life expectancy calculates the life expectancy cross-sectional using the mortality (and disease or disability) numbers of a given year. This can be done for any

simulation year by choosing from the pull-down menu “year”. When changing the age, then the plot shows the further life expectancy.

The menu “life-years gained or lost” (only available in cohort mode, and only for scenarios that use the same transition-rate file as the reference scenario) gives the option to calculate a DALY type measure or the (weighted) life years gained or lost compared to the reference scenario. The option “DALY (1 year exposure change)” gives the number of years with disease/disability (or disability-weighted years when daly-weights are used instead of disability) gained in a situation where the risk factor prevalence of alternative scenario is in force for one year, and afterwards returns to the value it would have had in the reference scenario. The option “only for this age” gives the life-years gained or lost by a cohort that has the selected age at the start of simulation and is followed until all have died. The option “for all higher ages” displays the sum of all future years gained or lost by the total population at the start of simulation that has the selected age or higher. Also in this case the population is follow until all have died.

Write output

Click on the tab “Write output”. On this screen three different decisions can be made. First, you can choose to the type of file to export. This can be the population at each simulation year (first 6 options), or the calculated life expectancies. In the first case, data can be exported as excel readable XML or CSV. Excel readable XML files are written in a special format that, when opened with MS Excel, distributes the data over different worksheets. To open these files, right click on the file in window Explore, and chose

“open with” and then chose MS Excel. CSV files use the CSV format, which can be imported by many statistical packages for further processing, including MS Excel.

In both cases, two types of data are available: “per year of simulation” (or “yearly data”) or “by cohort”. The first summarized the population data by age and risk factor value as this is in each year of simulation. The second summarizes the population data by age and risk factor value at the start of the simulation. When newborns are included in the simulation, the yearly data include the data of newborns, the cohort data do not include newborns. The excel readable XML files are always in the form of a separate file for each scenario. For the CVS format one also has the choice of exporting all data to a single file (which includes a column indicating the scenario).

The second option allows choosing to export the data “separate for men or women” or “total population”. The third option determines whether diseases are shown separately (“per disease”) or with more detail within diseases clusters (“per combination of diseases”) in the exported output. In the latter case, whenever there are clustered diseases (i.e., diseases that are related by a relative risk from a disease on a disease), the prevalence of each combination of disease is given. Thus when diabetes and IHD are clustered, the output presents the prevalence of IHD only, diabetes only, and having IHD and diabetes simultaneously. When clicking on “write data”, you can choose a file name and file location where the raw output is saved.

TIP: The default directory for saving output files is the “result” directory under the simulation. While this is a logical place, having many excel-readable xml files in this directory will slow down starting up DYNAMO. Therefore, saving these files in another directory (outside the DYNAMO working directory) is recommended.

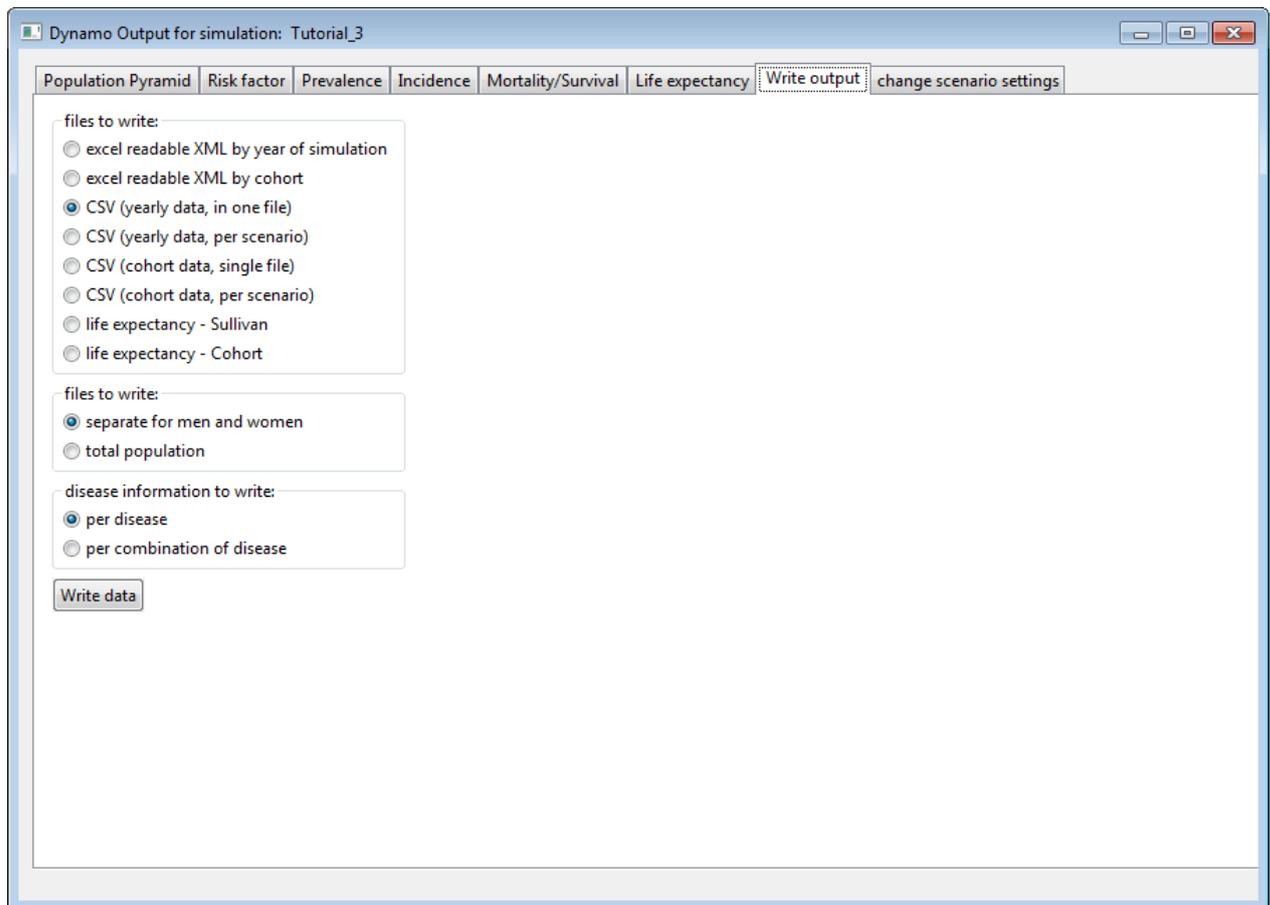


Figure 16: write output screen

Change scenario settings

The “change scenario settings” tab allows adjusting the intervention scenarios even after the simulation has been run. Four different choices can be made for each of the interventions scenarios. The success rate of the intervention can be adjusted between 0 and 100 percent. When the success rate is 0 percent, the output shown for the intervention scenario is exactly the same as the reference scenario, with 50 percent success rate the intervention scenario is average between the intervention scenario

setting and the reference scenario setting. Furthermore, the minimum and maximum age for which the intervention has been successful can be chosen and if both or only one gender is affected.

In the example of “Tutorial_3”, a maximum age of 50 would mean that the in the intervention scenario (“UK_Prevalence”) only the people of 50 and under would be switched from the Dutch BMI-prevalence to the UK BMI-prevalence. Note that the sliders and buttons on this tab are only present if one or more alternative scenarios are included in the simulation. The tab is empty when only a reference scenario is run.

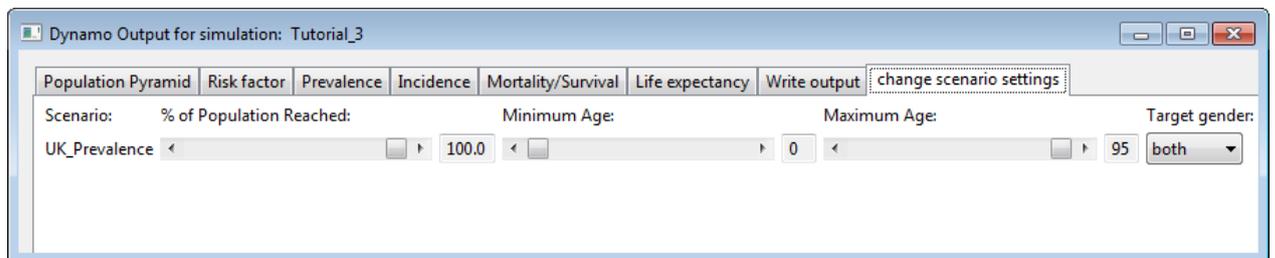


Figure 17: Change scenario settings Tab in output screen (detail)

Inspecting the model parameters

The DYNAMO model uses the input data to calculate parameters (like disease incidences in those with a relative risk of 1 (baseline incidence), the mortality that can be attributed to a particular disease, or intermediate disability parameters (baseline ability). When running the model, these parameters are stored in a directory “parameters” above the “results” directory. After running the model, the value of these parameters can be inspected, by opening the directory and right clicking on the name of the parameter file one wants to inspect.

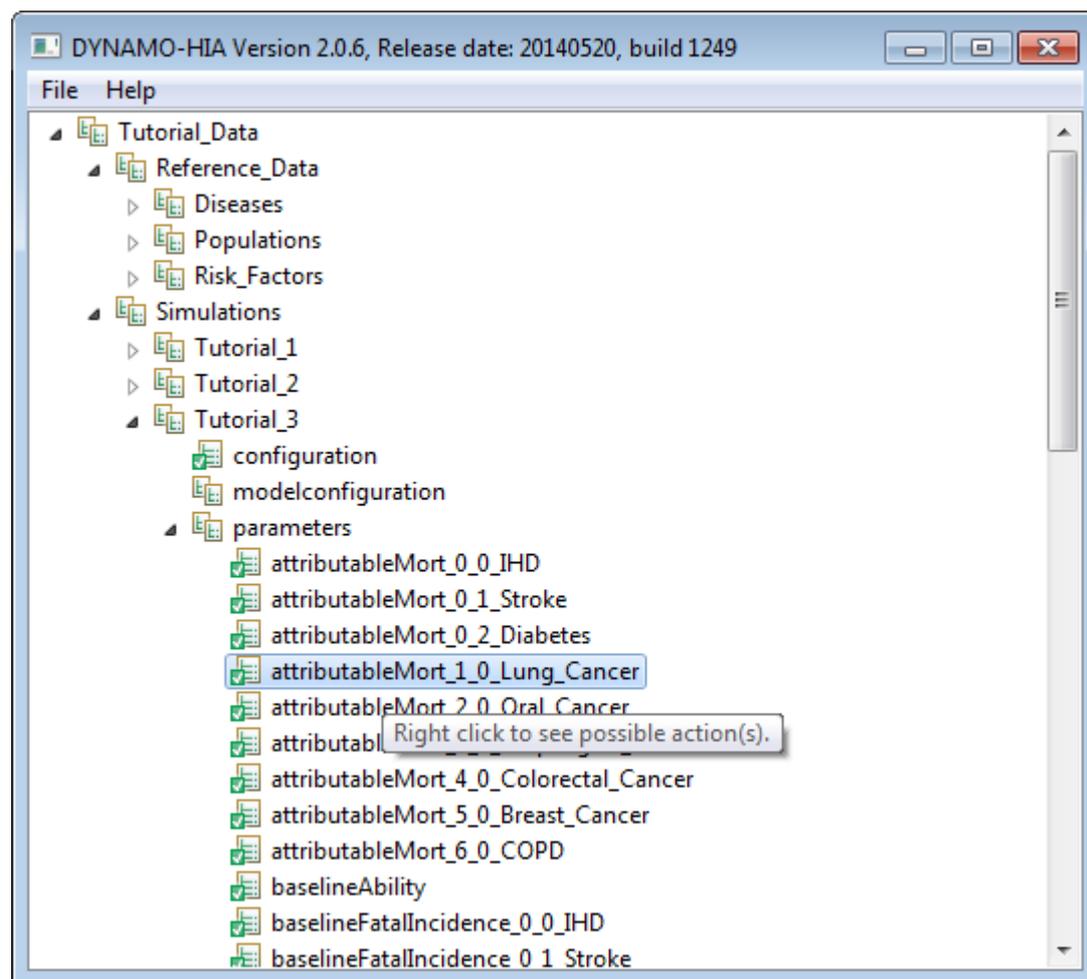


Figure 18: Selecting a parameter file for inspection (detail)

In some situations, the other mortality that will be used in the model could not be made exactly equal to the difference of the total mortality and disease-related mortality as given by the user to the model. In this situation a file “otherMortData.csv” is written to the “parameters” directory in order to make further inspection possible. This file cannot be seen in this view, but can be opened with for instance excel. After opening this file with excel, use data → filter → autofilter to activate the autofilter. Then, after choosing an age and a sex group in the filter box, and selecting columns C to G, the chart wizard can be used (option XY(scatter)) to plot the data for a particular age and sex combination (figure 16). Data included in this file are:

- Risk factor: depending on the type of risk factor used, this is category number of the risk category (categorical risk factor), the value of the continuous risk factor (continuous risk factor), or the duration (compound risk-factor). For the compound risk factor the value zero is assigned to all non-duration categories
- otherMort: the difference between the total mortality as specified by the user, and the disease related mortality
- otherMortfitted: other cause mortality used by the DYNAMO-model
- diseaseMort: disease related mortality (from the specified by the user in the excess mortality file) used by the DYNAMO model
- totalMort: total mortality as specified by the user

When the effect of other mortality counter-acts the effect of disease-related mortality, the effects on overall mortality are unpredictable. If this happens for more than a few age-groups, we advise not to include a relative risk on mortality in the model. For continuous and compound risk factors see also pages 87 and 88 respectively for further interpretation.

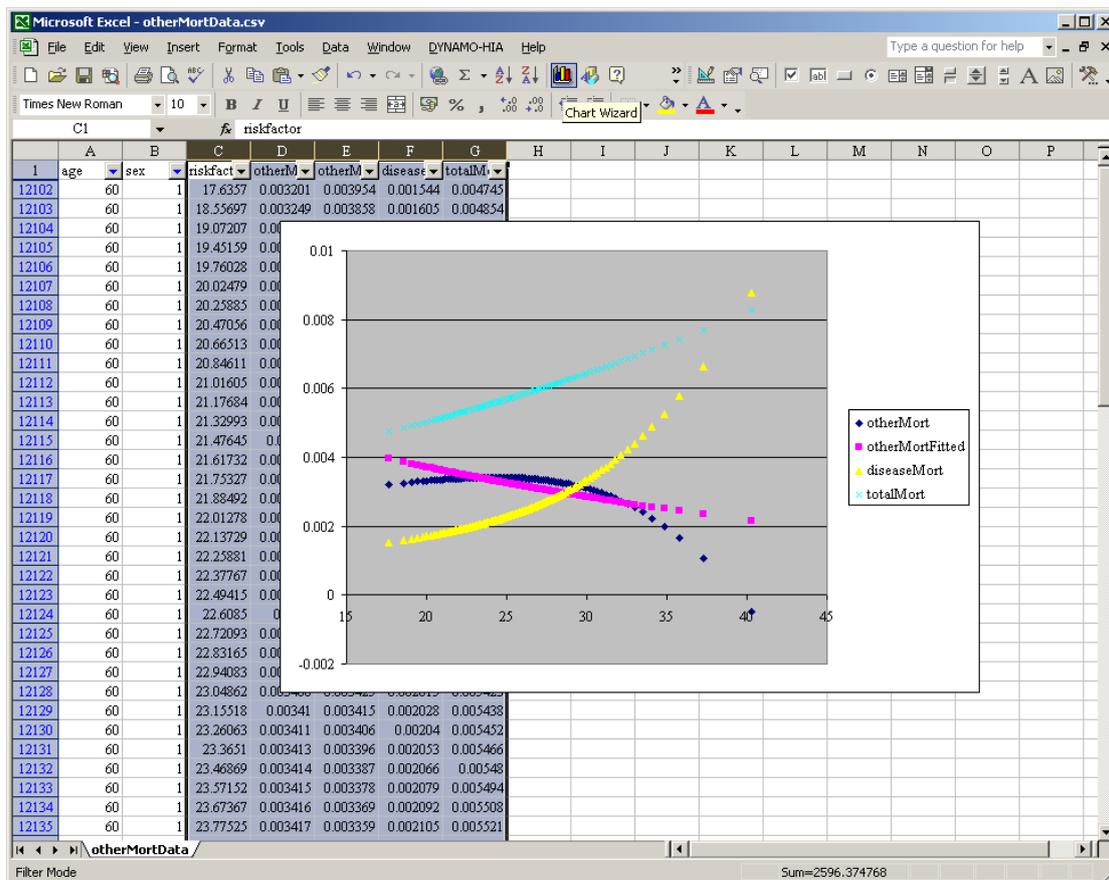


Figure 19: Inspecting the other cause mortality as used by the model in Excel.

In this example, the other mortality (dark blue) declines with increasing risk factor values, because disease related mortality (yellow) has a steeper increase with risk factor values than all cause mortality (light blue). At very high risk factor values the disease related mortality is higher than the all cause mortality. This is not a very realistic situation, and one might want to reconsider the input to the model causing this. These inputs are: the relative risks for all cause mortality (determining the steepness of the light blue curve), and the prevalence and excess mortality of the diseases, as well as the relative risks of the risk factor on the diseases (determining the absolute height and the steepness of the yellow curve). If nothing is done, DYNAMO will use the purple other mortality. In that case the all cause mortality used in the model (= sum of the yellow and purple curves) will be higher than the inputted all cause mortality for low risk factor values, but higher for high risk factor values.

Entering Data

This chapter gives detailed description on how to enter reference data.

DYNAMO-HIA needs two kinds of inputs from the user: *Reference Data* and *Simulations*. The *Reference Data* consists of data on *Diseases*, *Populations*, and *Risk Factors*. Data can be entered and manipulated in several different ways. The exact procedure depends on the data at hand. Different diseases, population, or risk factors can be specified or the same diseases, population or risk factors can be specified in (slightly) different ways, such as discrete or continuous definition of the same risk factor. The input for *Simulations* configures the desired scenario and initiates the simulation run. In this menu the user chooses the population, the risk factor and the diseases to be simulated.

Navigating the Data Tree

This section gives an overview of the mechanics navigating the data tree and how to access a certain section of the input data. It might be skipped by more experienced users.

The data-tree is the main interface to input, organize, and track the data that are being used in DYNAMO-HIA.

The data-tree is being set up in the chosen working directory and consists of two main folders: *Reference Data* and *Simulations*. In the folder *Reference Data*, all the input data needed to run a simulation is being stored. In the folder *Simulations* the configuration files for the different simulation and the resulting simulation results are being stored. Within the directory *Reference Data*, three sub-directories exist: *Disease*, *Populations*, and *Risk_Factors*.

When left-clicking on a node with a plus sign right next to a directory name, the directory tree expands: The node changes now from a plus sign to a minus sign and further directories are listed. In Figure 17 an example is given: First, only the folders *Reference Data* and *Simulations* are visible. When left-clicking on the node next to *Reference Data*, the view expands. Now, the directories *Disease*, *Populations*, and *Risk_Factors* become visible.

When, for example, left-clicking on the node next to the directory *Disease*, it expands as well and further sub-directories (when already existing) become visible. In the case that the user wishes to create a new disease that should be included in the simulation, a new directory has to be created. The new disease will be created by right-clicking on the directory *Disease*. A context menu with the single option *New Disease* will pop up. When left-clicking on the option *New Disease*, a naming window will appear. In this window a name for the new disease can be assigned (see appendix B for advice on naming⁴). When pressing the *OK-Button*, the sub-directories needed to store the data for a disease are created. Those sub-directories become visible when left-clicking on the node right next to the chosen disease name.

The procedure is the same for the directories *Populations* and *Risk_Factors*. With a left-click on the node the view is expanded and further directories – when already created – become visible. With a right-click on the directory name a context menu pops up to

⁴ DYNAMO-HIA has some rules that must be obeyed in naming : no spaces or hyphens (-) can be used in any names. Also the names “totaldisease” and “disability” are not allowed. (If you would want to define disability as a disease, use another name, like disabilityAsDisease)

allow the creation of new diseases, populations, or risk factors, respectively. Similarly, a new simulation can be specified by right-clicking on the directory name *Simulations*.

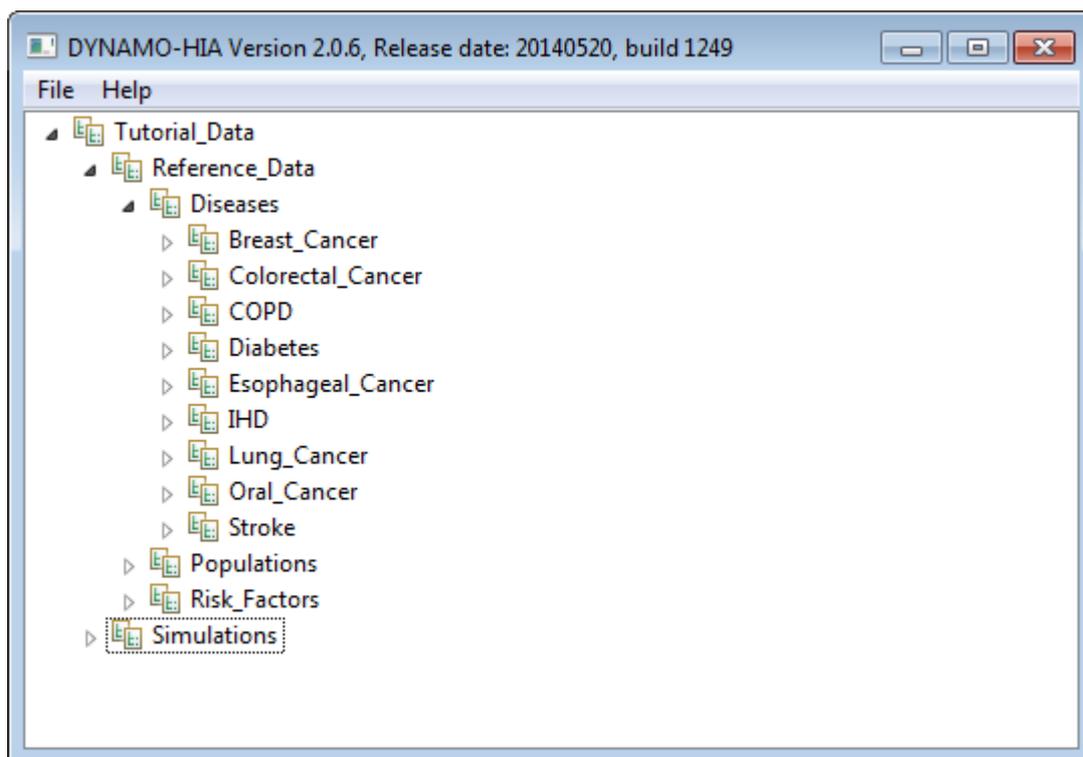
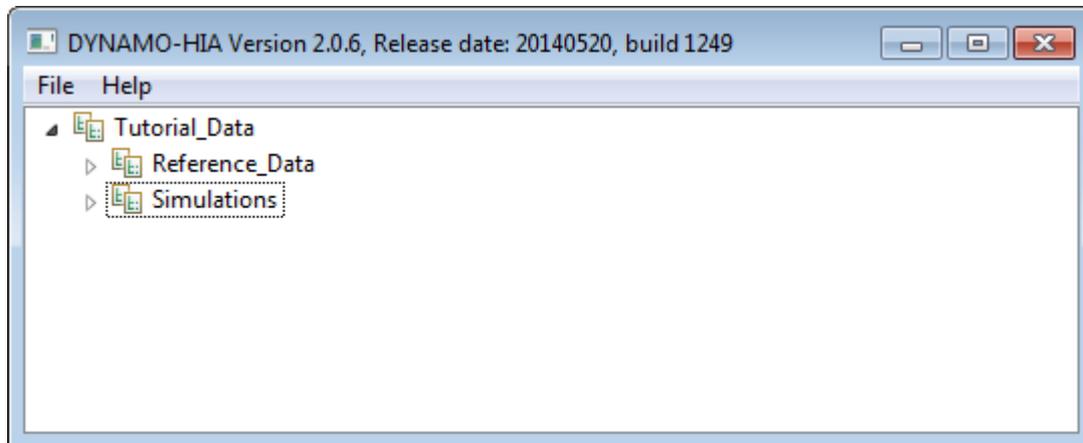


Figure 20: Data Tree Navigation

Example: Data Tree with all directories collapsed (upper panel), Data Tree with the directory Disease expanded (lower panel)

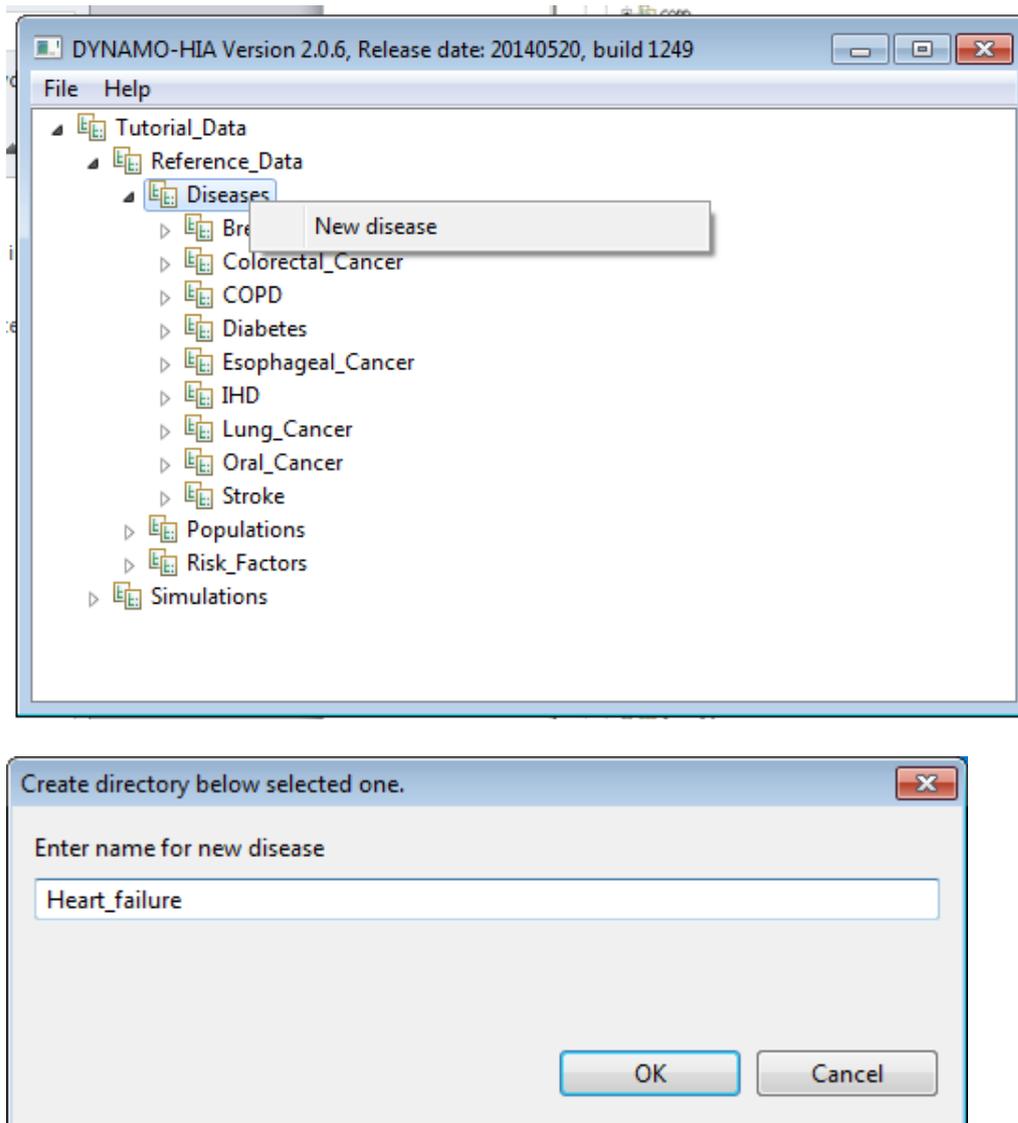


Figure 21: Data Tree: Example of creating a new disease directory:

Data Tree showing the context menu that appears right clicking on the directory Diseases (upper panel),
The naming menu for a new disease (lower panel)

General Mechanics of Data Entry and Manipulating

For entering data into DYNAMO-HIA three different ways exist:

1. Entering by hand into the respective data window

2. Using the import function
3. Copying a file into the working directory

We outline here the general mechanics and describe the idiosyncrasies of the respective data windows below.

Entering by hand

For entering the data by hand, open the respective data window (e.g. *Overall DALY weights*). Enter the desired number in the appropriate field, i.e. by age and sex. To save the results press the *Save* button at the bottom. This can be done repeatedly while entering a large amount of data to ensure that data no is going to be lost in case of a malfunction of the computer (e.g. an electricity black-out). When finished with entering data, the *Save and Close* button closes the window while automatically saving the data. The *Close* button closes the data window without (!) saving the data. DYNAMO-HIA verifies while entering and saving the data whether the entered figure is consistent with the required input, e.g. not negative when a probability is required and so on, and gives a warning message. This, however, does not safe guard for entering wrong data; it only assists in finding errors.

Using Excel templates and the import function

Together with DYNAMO-HIA, Excel templates are available. Those exist for the different data types needed for DYNAMO-HIA and can be used for storage outside of DYNAMO-HIA. The advantage of storing in Excel files is easy checking of the data by making graphs or taking sums. The excel files contain macros that export the content of

a given Excel file (e.g. overall DALY weights) into an XML-file. These XML-files can be easily imported into DYNAMO-HIA.

If DYNAMO-HIA has been installed using the installed, the excel notebooks containing these macros can be opened from the start menu (DYNAMO-HIA → Macro). Otherwise they are included in the DYNAMO-HIA.zip file that can be downloaded from www.dynamo-hia.eu for manual install. The working of the Excel macros is explained on the first sheet of each excel notebook. In the help text of each DYNAMO-HIA reference data screen (on the right side of the screen) it is indicated which Excel notebook is needed to produce a dataset needed by that screen.

The macros were developed for Excel 2003. However they also work in Excel 2010-2013. However, in that case one should allow content. The DYNAMO-HIA addition then is found under the ribbon tab: add-ins.

Importing net transition rate files from the parameter directory

If net transitions are asked from the model, the input file does not contain data, only the message that net transitions should be used. These will always be the net transitions of the reference scenario. However, when running the model, it makes a net transitions matrix for the simulation module, and stores this as an XML file in the parameters directory under the simulation. For categorical (and compound) risk factors, this XML file has the same format as a user specified transition matrix. Therefore it is possible to import these files as user specified transition matrixes.

For instance, if you would want an alternative scenario to use transitions that are the net transitions of the prevalence rates of this alternative scenario, you can do so by first running this scenario as a reference scenario, and then (after the model has run) use the import function to import these net transition rates from the parameter-directory.

When the macro in Excel has been used to create an XML-file, go to the respective data window in DYNAMO-HIA. Then press the Import button. The file explorer opens.

Choose the XML-file to be imported and open it. The data will appear in the data window and the data window can be closed using the *Save and Close* button. When the XML file does not conform to the required data specification for the respective data window (e.g. the mortality rate template was used but overall DALY weights are required), an error message will appear.

Copying files into the working directory

This approach is only recommended for computer-savvy users.

DYNAMO-HIA stores the data using a fixed directory structure containing XML-files. When the XML-file conforms to the specification of the respective directory, it is accessible by DYNAMO-HIA. Hence, one can just copy such a XML-file or a whole directory containing several sub-directories with the respective XML-files into the working directory. However, this may lead to serious mistakes destroying the required file structures. Therefore we strongly recommend using the import option.

Some common mistakes that lead to problems in the working of the program that have occurred when making working directories “by hand”:

- No capitals at the right places in the directory names (the program cannot find diseases / risk factors / populations which seem to be present in the interface)
- The names of the relative risk files do not contain the required “-riskfactorname” as final element: the files are not recognized by the program
- The files in the population directory do not have the prescribed name (i.e. size, newborns, overallmortality, overalldisability)
- The extension .xml is not given in lower case
- Unallowed names (totaldisease, disability) are used as diseasenames

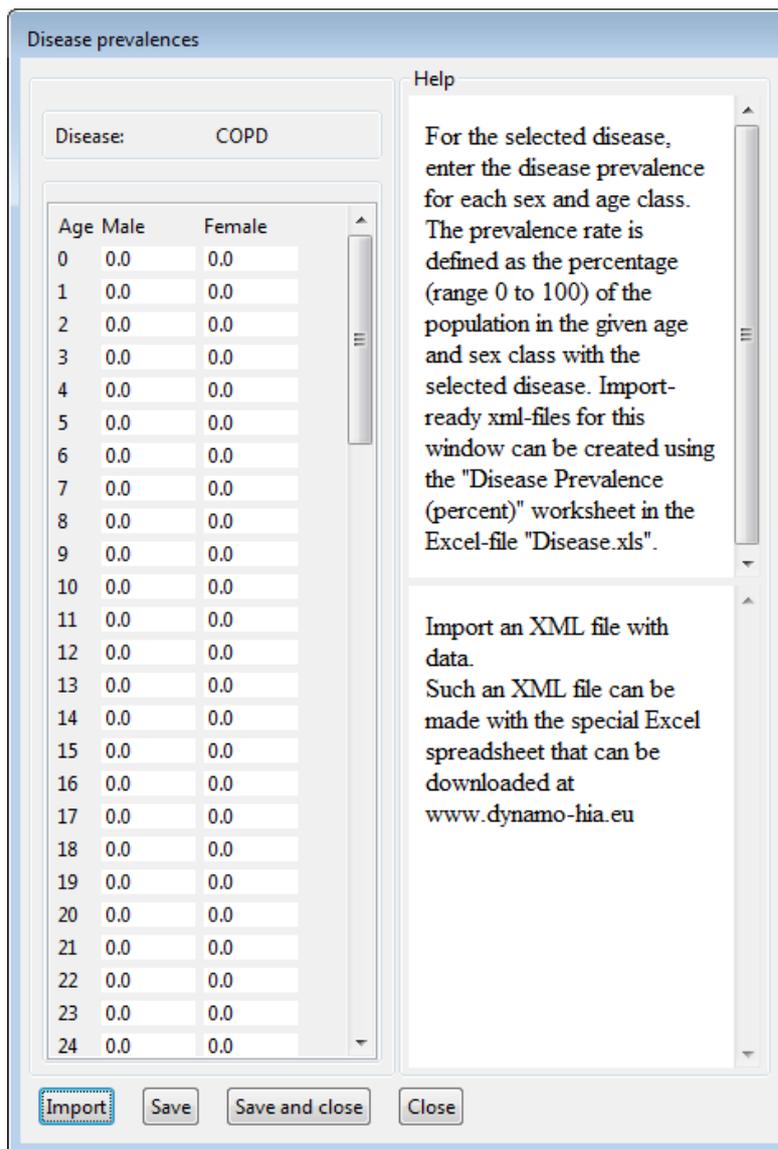


Figure 22: Example of data entering window

Example of data window (here: Disease Prevalence) (upper panel)

Saving button data window highlighted (lower panel)

Specification of reference and intervention scenario's

The most important aspect of running health impact calculation, is to specify the reference and intervention scenario. The challenging part is that, as DYNAMO-HIA is a dynamic model, one needs to specify not only the current simulation, but also what will happen with exposure in the future. The latter should be given to the program in the form of “transition rates”.

In DYNAMO there are three options to specify the future transitions:

1. User-specified transitions: the user provides data on transitions between the risk factors categories (e.g. smoking start probabilities and quit probabilities rates, or on trend for continuous exposure (e.g. increase in mean BMI of 0.02 for each age year).
2. Net transitions: The user assumes that the age-specific prevalence of exposure in the population will remain the same (thus prevalence by age and sex does not change). This approach is very similar to the use of period life expectancy, where for a newborn the currently observed age-specific mortality pattern is assumed to remain valid. This approach ignores any cohort effects. This approach is named “net transitions” in DYNAMO-HIA, because DYNAMO derives the minimum transitions that are needed to keep the age-specific prevalence unchanged in the future. DYNAMO can only calculate net-transitions for the reference scenario. In the case net transitions are also specified for alternative scenarios, DYNAMO uses the net transition rates calculated from the prevalence of the reference scenario also for the alternative scenario. In other words, it assumes that the future dynamics of the risk factor remain the same. We also describe on (see page 65) how to make net transition rates for the reference scenario.

3. **Zero-transitions:** Persons are assumed keep the exposure in the baseline year throughout their life until they die. Hence, persons having a normal weight at baseline keep that during the entire period or until they die. This approach is named “zero transitions” in DYNAMO, as there are no transition between risk factor categories or changes in mean BMI in the future when persons age.

To specify what is expected in risk factor exposure due to the policy or intervention (=intervention scenario), the user can change the following as compared to the reference scenario:

1. Change the baseline exposure, that is the prevalence rates at the start of the simulation
2. Change the future transitions
3. Change both baseline exposure and transition.

It is important to realize that, due to dynamic behavior, generally in the long run other prevalence rates are realized than that where given at baseline. In the long run, the prevalence rates will revert to a kind of “steady state” that is determined only by the transition rates. So if the same transition rates are used for two scenarios, in the long run the prevalence rates will become the same. An exception is when net transitions are used: Net transitions do not exhibit this type of dynamic behavior (see Kasstele, J., et al. (2012). "Estimating net transition probabilities from cross-sectional data with application to risk factors in chronic disease modeling." *Stat Med* 31(6): 533-543.)

Running DYNAMO in batch-mode

It is also possible to run multiple simulations one after the other outside the graphical Dynamo-HIA software (under Microsoft Windows), that is, in batch mode. This can be done by starting a batch job from the windows command line as described below. It can only be used to run Dynamo-HIA from other applications.

To do so, one must first prepare a work directory for the simulations, that is a directory containing a reference directory with data, and a simulation directory containing the multiple simulations to be run (Figure 20). Since the simulation run is identical to the run initiated from the Dynamo-HIA graphical user interface, the simulations can be tested from the graphical user interface before a batch-run is attempted.

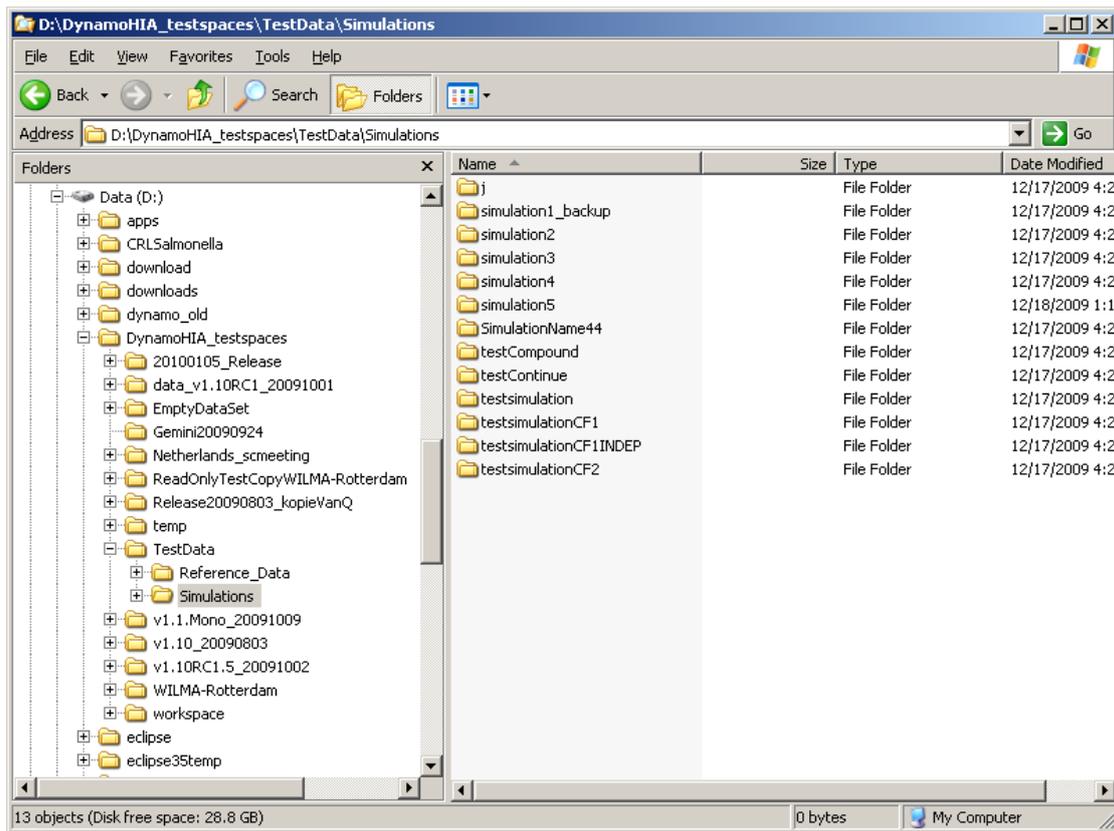


Figure 23: A work directory has to be prepared containing the simulations to be run

Now use a plain text editor (notepad, vi ...) to create a text file containing the names of the simulations to be run (Figure 21).

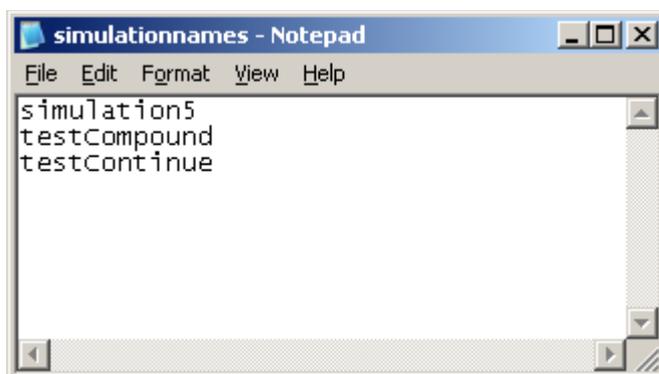


Figure 24: Example of a text file containing the names of the simulations that should be run in batch-mode

This file must be placed in the base-directory at the same level as the “Reference-Data” and “Simulations” directories (Figure 22). Multiple files can be created there.

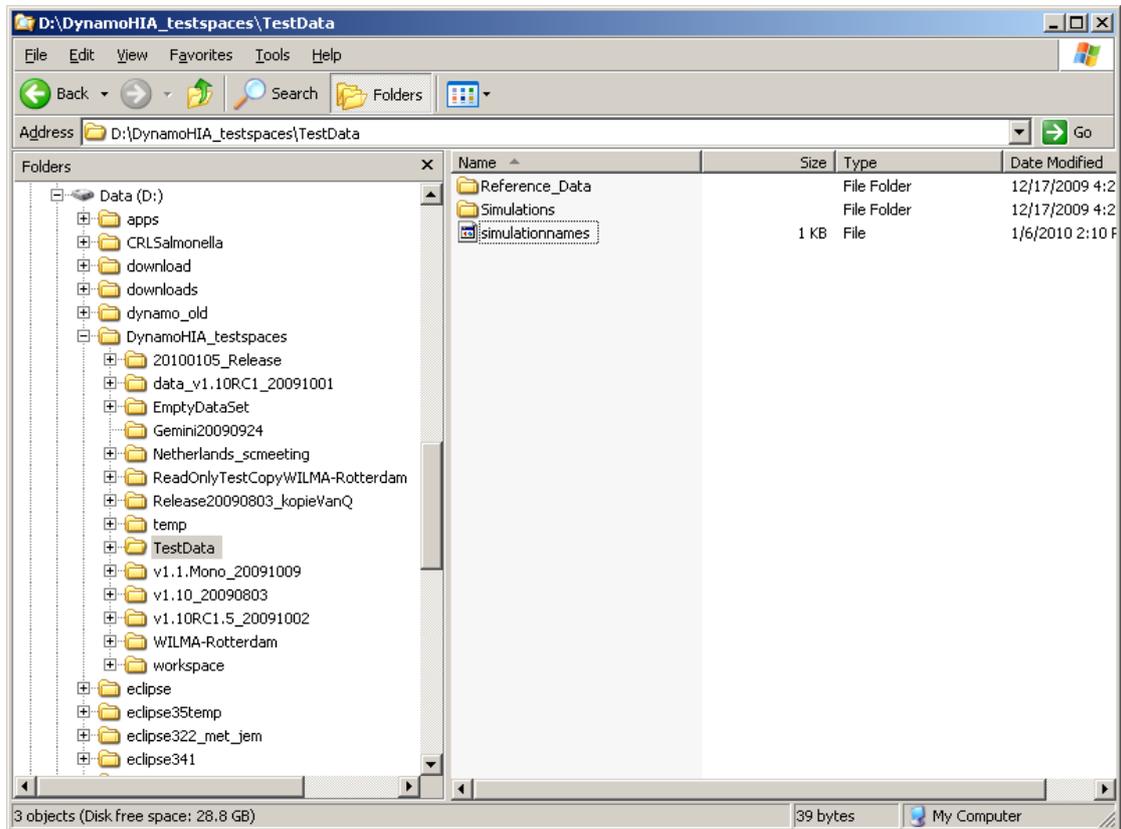


Figure 25: Place of the text file containing the names of the simulations that should be run

Now open a command line window. To do so, first click the Windows Start menu (located at the very lower-left corner of your computer's desktop) and select "Run...". Then if you are using Windows XP or Vista or Windows 7 or 8, type cmd into the Run box and click "OK". You could also type cmd.exe. Otherwise, if you are using an older version of Windows, type command into the Run box and click "OK". You could also type command.exe. (Figure 23)

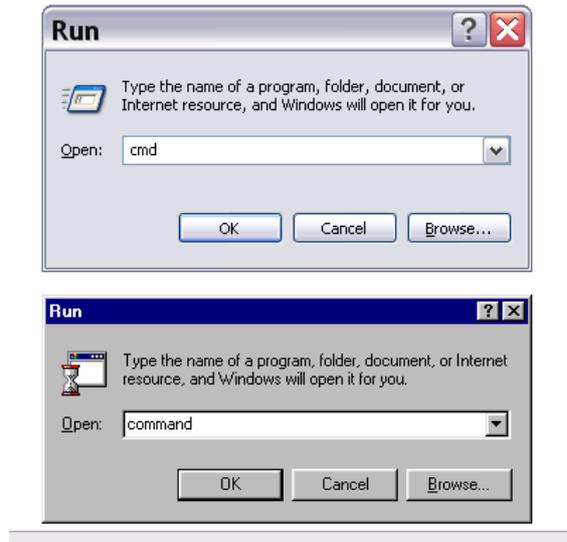


Figure 26: How to open a command window

Now find to the “eclipse” directory inside the current release (with standard installation this is in the “C:\Program Files\RIVM\DYNAMO-HIA\ Dynamo-HIA Application”) directory. You have to make this directory the "current" directory, which you can do by using the cd command ("cd" is short for "change directory"). With the standard installation you do so by typing:

```
cd c:\programfiles\RIVM\Dynamo-Hia\Dynamo-HIA Application\eclipse
```

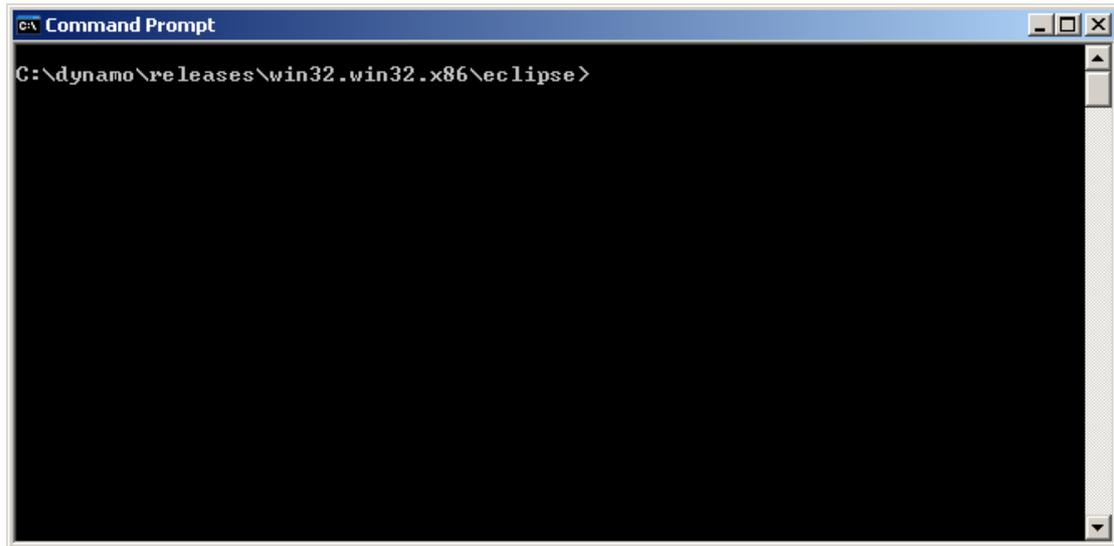


Figure 27: Command window, with the eclipse directory as the current directory

Then enter “runbatch “ plus the path to file we made above.

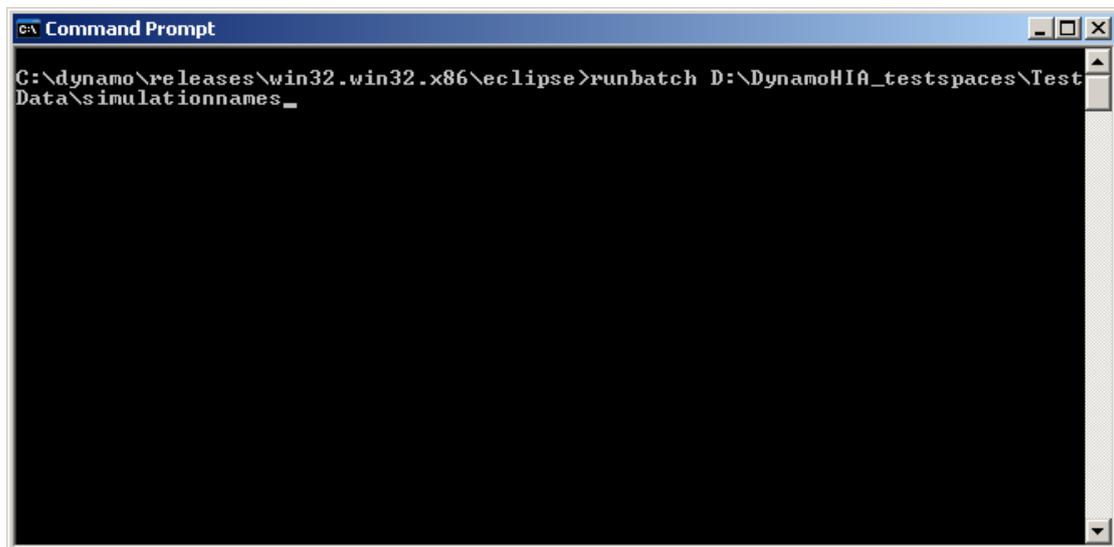


Figure 28: Entering the command running DYNAMO-HIA in batch mode

Press <Enter> and the simulations will be run. Output of each simulation will be written to the file “batchout.csv” in the results directory of the simulation. This is a csv file using ; as separator. Also an results.obj will be made, which can later be inspected with the graphical user interface.

Alternatively, the program could be run directly from other programs. Here we exemplify this by given the code on how to run DYNAMO-HIA from R.

Follow the same steps to prepare the data. Then in R, set the work directory to the “eclipse” directory (e.g.:

```
Setwd(“C:\\Program Files\\RIVM\\DYNAMO-HIA\\ Dynamo-HIA Application”)
```

Then run the batchrunner with:

```
system.time(shell("runbatch.bat D:\\DYNAMO_testspaces\\TestData\\simulationnames  
))
```

Note: the pathname should not contain any spaces, and one should use \\ (and not /) as directory separators.

Simulation Methodology

We briefly summarize the simulation methodology below, while this methodology is described in detail in the document “Detailed description of DYNAMO-HIA calculations” which is also included in the installation package. The simulation methodology is also described in two papers, which were submitted for publication when finalizing this manuscript. Below we first give an intuitive explanation of the core methodology within DYNAMO-HIA, and a series of figures illustrating the methodology and that we think are helpful to gain more insight. Second we will discuss in more detail some of the consequences of our modeling approach, addressing specifically the consequences of several choices that are open to the user.

Model Core

DYNAMO-HIA is a Markov-type model based on a multi-state model (MSM). The change of the current state depends only on present characteristics (i.e. age, sex, risk-factor status, and health status). The MSM is implemented as a *partial micro-simulation* combining a stochastic micro-simulation to project risk-factor behavior with a deterministic macro approach for the disease life table. In the micro simulation module a large number of distinctive risk-factor biographies are simulated: Given the age and sex-specific transition probabilities between risk-factor states, the risk-factor status of each simulated individual is updated in annual increments (see Figure 26 for details). In the macro module, as many disease life tables as there are risk-factor biographies are constructed. These disease life tables are able to account for competing risks and multiple morbidity. The exact configuration of the disease life tables, i.e. the number

and kind of diseases, can be specified by the user. For every risk-factor biography, the probability of disease incidence and mortality over time is calculated, accounting for the current age, risk-factor and disease status. These biography-specific life tables are calculated for every cohort, i.e. all individuals that are born in the same calendar year. For example, for a cohort of newborns first the risk-factor biographies are projected and then disease life tables are calculated. Older cohorts, i.e. born before the first simulation year, start out having the disease prevalence specified in the input data, which is then similarly updated. Population values are obtained by aggregating the individual biography/diseases life tables: either across cohorts at a given simulation time point to obtain period measures or along cohorts to obtain cohort specific measures. The split into a micro and a macro module is done purely for computational convenience and micro and macro-simulations yield the same result when used with the same data. However, time and memory requirements in macro simulations rise exponentially when the number of simulated states increases and a micro simulation – unlike a customary multi-state life table – does not require the a priori specification of all theoretically possible combinations of diseases/risk-factor states, but only those states that are actually occupied. But for simulating rare events – such as lung cancer at young ages – micro simulations require the simulation of a large number of individuals, offsetting the savings in time and memory requirements.

The epidemiological model uses relative risks by risk-factor class, i.e. incidence in exposed risk-factor classes is a multiple of the incidence of the non-exposed. The total mortality, i.e. population level mortality by age and sex, is being decomposed in the mortality due to the diseases included in the model and other cause mortality. This decomposition assumes additive mortality: the total mortality rate in the population is explained as the sum of the mortality rate of the included diseases and other-cause

mortality, i.e. mortality from all causes/diseases that are not explicitly included in the model.

DYNAMO-HIA simulates the effect of a single risk factor on a population without migration. However, the categorical risk-factor can be used to partition the population in up to ten distinctive categories. For example, a population could be partitioned along a risk-factor – say, non-smokers and smokers – and socio-economic status – say, with college education and without college education, having in total four different groups. This could be used to assess a policy which is known to be more successful for people with certain socio-economic status. The possibility of partitioning the population can also be used to quantify the effect of an environmental hazard. In this case, for example, the population is partitioned according to their proximity to the hazard source – say, noise exposure or air pollution due to a new airport with 5% of the total population living less than 5km from the hazard source , 5% to 10% living less than 10km and so on. This requires of course sufficient insight into which part of the population is affected and knowledge of the relative risks of the modeled exposure level on the included diseases and total mortality.

A category may also stand for a combination of known risk-factors: For example, smoking status and BMI – smoking/non-smoking and normal weight / overweight / obese – could be modeled by partitioning the population into six distinctive risk-factor categories. However, it requires knowledge about the relative risk of the combined risk-factor class – say, relative risk of being obese and a smoker on the included diseases and total mortality.

Figures illustrating the DYNAMO-HIA methodology

risk-factor biography	Age								
	x	x+1	x+2	x+3	x+4				
1	N	→	N	→	P	→	P	→	O
2	O	→	O	→	P	→	N	→	N
3	P	→	P	→	N	→	N	→	N
4	N	→	N	→	P	→	O	→	O
5	N	→	N	→	P	→	O	→	O
6	P	→	P	→	P	→	P	→	P
7	N	→	P	→	P	→	P	→	P
8	N	→	P	→	O	→	O	→	O
9	N	→	N	→	N	→	N	→	N
10	N	→	P	→	P	→	N	→	N

N= Normal Weight, P=Overweight, O= Obese

Figure 29: Example of risk-factor biographies for a risk factor with three categories.

DYNAMO-HIA simulates individuals and projects their risk-factor biographies. In annual increments the risk-factor status is being updated, given age- and sex-specific transition risks. The age- and sex-specific risk-factor status determines the relative risk of a person to contract a disease or to die. DYNAMO-HIA allows one risk-factor per scenario. This risk-factor can be either categorical (up to ten categories), duration dependent (up to ten categories of which one is duration dependent, i.e. the risk on disease in this category depends on how long a person is in the category), or a continuous distribution (normal or log-normal, specified by entering mean, standard deviation, and, in the case of the log-normal, skewness).

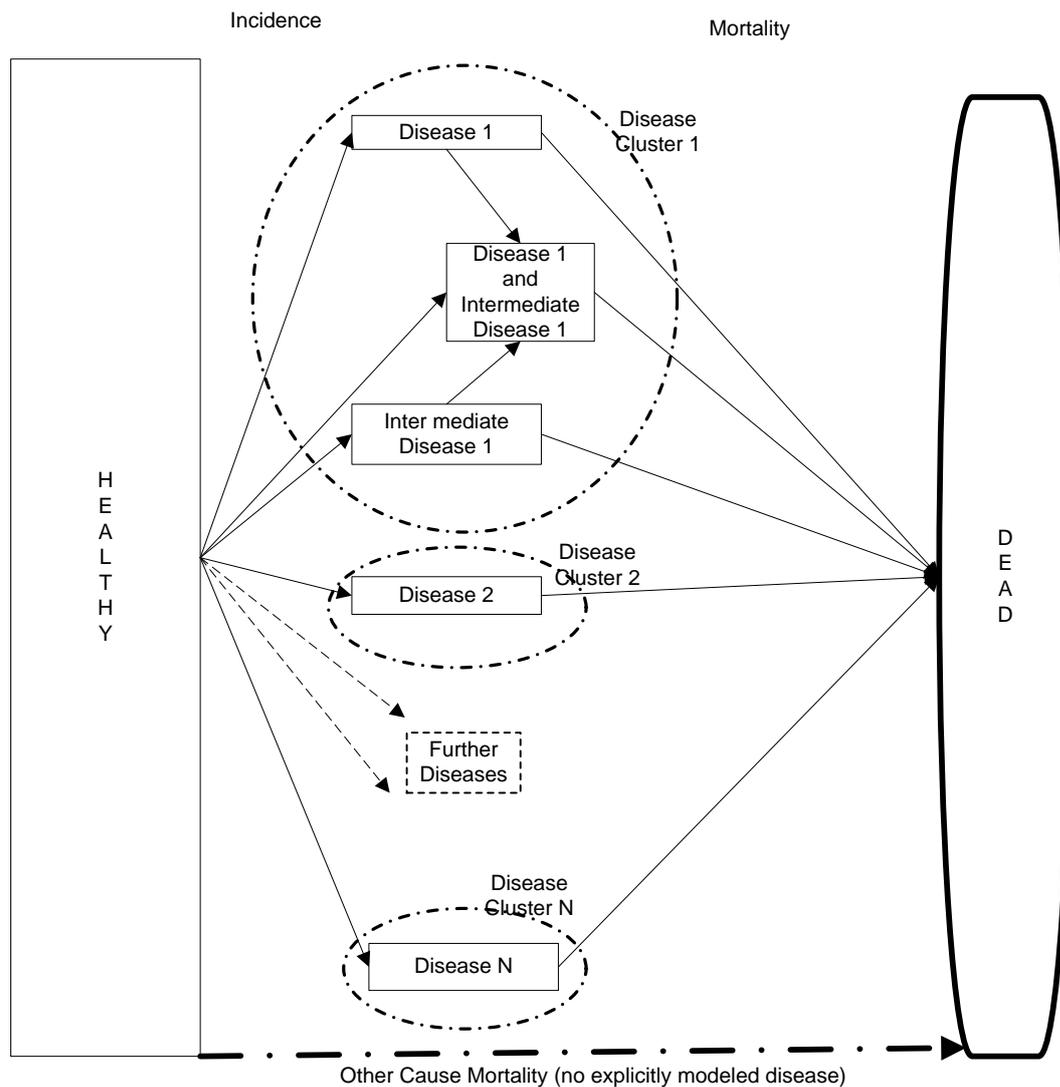


Figure 30: Stylized structure of disease life table

The disease life tables contain diseases clusters. Each disease cluster consists of one or more diseases. Within disease clusters, intermediate diseases - that increase the risk of getting another disease - can be specified (e.g. having diabetes increases the risk of getting IHD). All diseases are chronic diseases, i.e. excess mortality depends on age and sex and not on time since onset of disease. However, acutely fatal and/or cured fraction can be specified for diseases. The disease life table assumes independence between disease clusters. The user can freely specify the relative risks from risk-factor to disease, from risk-factor to death, and from intermediate disease to other diseases.

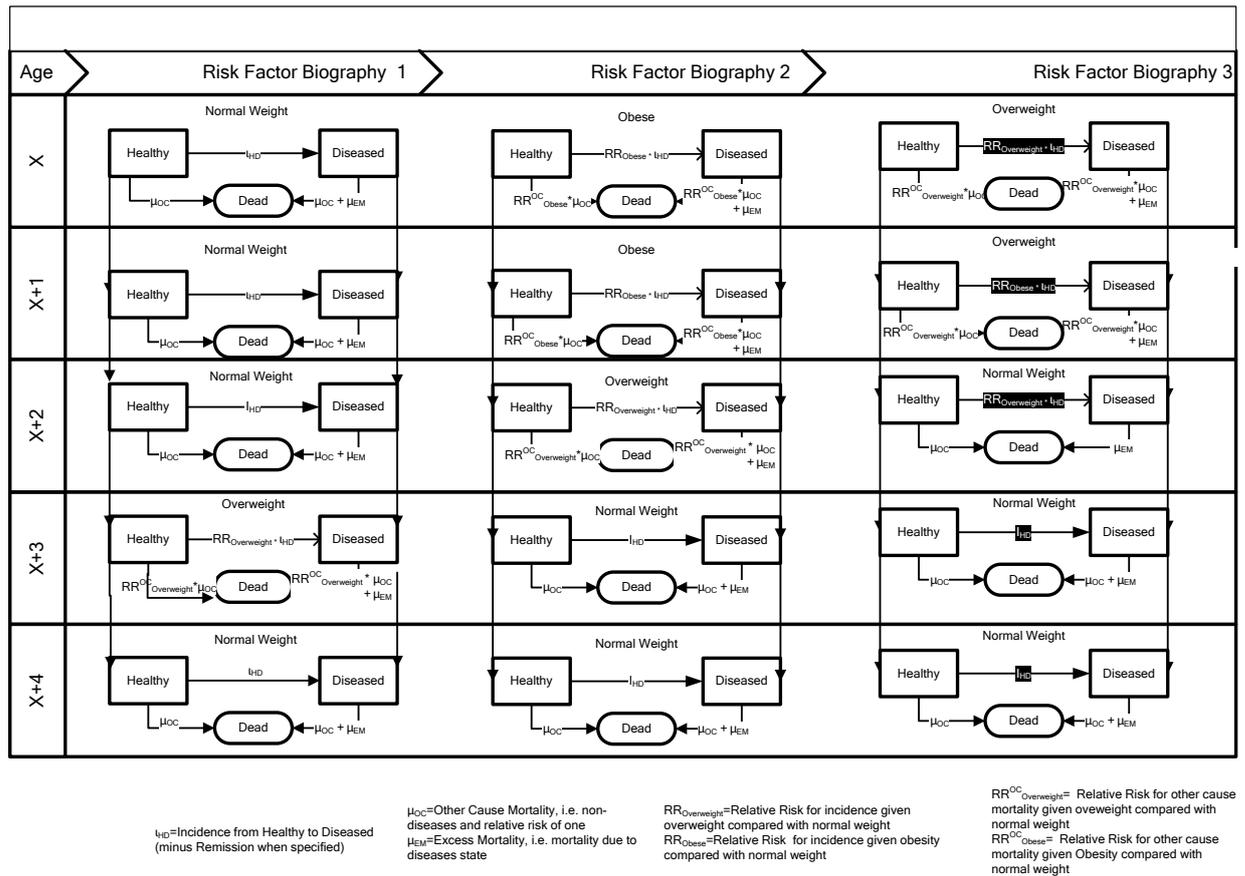


Figure 31: Stylized cohort life tables (with only one disease, three different biographies, and five time steps)

For every risk-factor biography, a disease life table is constructed. Diseases incidence, i.e. transition from healthy to a disease, equals the baseline incidence, i.e. incidence when in a risk-factor class with a relative risk of one for the specific age- and sex-category, times the relative risk due to the given risk-factor and diseases status (in the case of an intermediate disease). The transition from healthy to dead equals the baseline other-cause mortality of the healthy, i.e. age- and sex-specific total mortality rate minus the excess mortality rate of the diseases included in the disease life table, multiplied by the relative risk due to the given risk-factor status on other cause mortality. The transition from diseased to dead equals the sum of the excess mortality of the disease (given each and sex) and the baseline other cause mortality of the healthy, multiplied by the relative risk in the given risk-factor status. Remission is not explicitly modeled, but for diseases with cured fraction the excess mortality is zero in a “cured”, i.e. user-specified, fraction. Partly acutely fatal diseases, i.e. diseases with very high mortality immediately after contracting the disease while for those who survive this critical period the excess mortality only depends on age and sex, are modeled by specifying the fraction of the incidence cases that die immediately.

Important Notes on using the model

The DYNAMO-model carries out rather complex calculations. Not all details of these calculations are obvious from the users interface, and consequences of some of the choices that users can make are not always intuitive. Below we highlight some issues that users should be aware of.

Negative other cause mortality

The total mortality (as given in the population data) in DYNAMO is split into “disease related mortality”, that is the mortality due to any of the diseases that are in the model, and “other cause mortality”. The magnitude of the disease related mortality is mainly driven by the prevalence of disease (if there are more persons with lung cancer, more will die because of lung cancer), by the excess mortality and by the fatal fractions of the disease. With many diseases in the model, having high prevalence rates as well as high mortality, it is possible that the sum of the disease related mortality at a particular age exceeds the total mortality at this age. In this case the model will not run, but will ask you to revise the data.

When you specify in DYNAMO a relative risk on death for your risk factor, DYNAMO will attempt to make the total mortality at baseline (= start of simulation in the reference scenario) in each risk factor class equal to that given by that relative risk on total mortality.

This is done by first calculating how high the total mortality in the risk class will be, given this relative risk and the overall mortality rate in the population. Next this is compared to the mortality that is due to the different diseases in the model. In a risk factor class with a higher incidence of for instance lung cancer, the prevalence of lung cancer at baseline will also be higher, and thus mortality from lung cancer will also be higher. So disease-related mortality will be higher in risk factor classes with a higher risk on disease. After summing the disease-related mortality in each risk factor class, the gap between the total disease-related mortality and the total mortality as calculated from the relative risks on death is taken to be the “other cause mortality”.

This other cause mortality will differ for each risk factor class, and can become negative. In that case it is made zero, while simultaneously the other mortality in other risk factor classes is decreased in order to retain the correct overall population mortality. If other mortality has to be made equal to zero in more than 30% of the population, a warning is given. In all cases, the estimated mortalities (disease-related and other cause mortality) are written to the “othermort.csv” file in the parameter directory, so that they can be inspected by the user. This is especially important for continuous and compound risk factors, where a parametric function is fitted to the other mortality before using it (see page 87 and 88).

It is important to note that in cases where the relative risk on death calculated from the disease information is higher than the relative risk on death as given directly by the user, the algorithm in DYNAMO lowers the other cause mortality in this risk factor class. In other words, it tries to compensate the too high disease-related mortality by a lower other cause mortality (compared to other groups). Only when this is no longer possible

(because other cause mortality in this class is already made 0), the relative risk on death will depart from relative risk on death as given by the user.

This can have counter-intuitive effects when running scenarios. This is due to the fact that the dynamics of disease-related mortality is slower than that of other cause mortality, as for disease-related mortality to steps are required: getting the disease and dying from it. This effect takes more time to develop than mortality from the one step process of dying from other cause mortality. We therefore advise caution with simulations that have negative other mortality warnings. Also, such warnings indicate that the relative risks on total mortality is already covered by the diseases in the model, and thus might be superfluous, so that a model that does not contain a relative risk on death might be preferred.

A good check in case of these warnings is to run the simulations also without a relative risk on death, and see whether conclusions remain the same.

Using continuous risk factors

When using continuous risk factors, the program assumes that the prevalence data have been smoothed over age. This is especially crucial for the standard deviation, as the program increase the variance of the risk factor over time when the standard deviation is increasing with age, but is not able to handle decreasing variance of risk factor in a similar way. When data are not smoothed, this means that the changes between years are too large, and as all negative changes are ignored, there will be considerable bias. Although this would not directly influence the average risk factor value, the exponential relations between risk factor value and disease incidence and other cause mortality will make that it does influence disease incidence and mortality.

Interpreting graphs of disease prevalence by risk factor level over time

The basis of the DYNAMO model is that in each scenario at time 0 (the starting year) either the risk factor prevalence, or the risk factor transition rates, or both are changed compared to the reference scenario. From that moment on, incidence rates and mortality rates will be based on the new risk factor levels. Disease prevalence, however, is a stock variable: it is the result of past incidences. This means that at the start of follow-up, the disease prevalence in all scenarios will be equal to that of the reference scenario, and that over the course of time the prevalence will diverge, as the number of new cases will be determined by the new risk factor status of subjects in the new scenario situation.

The consequence of this is that graphs of disease by risk factor level will show differences in disease prevalence rates between scenarios: As an example, take a scenario that changes part of the smokers into former smokers. In that case, the former smokers in this scenario will be a mixed group of subjects that were already former smokers, and of smokers that under the scenario were changed into former smokers. The latter will at time 0 still have the same disease prevalence of smokers, and so the disease prevalence in this mixed group will be higher than that of former smokers. In contrast, the former smokers in the reference scenario will all have the disease prevalence of former smokers. The result is that former smokers in the alternative scenario will have a higher disease prevalence than former smokers in the reference scenario.

The only exception to this rule are newborns: Newborns are given directly the prevalence of the alternative scenario.

Selective mortality and calculating net transition rates.

When net transition rates are calculated, the program uses the relative risks on death to take account of the effects selective mortality. Selective mortality implies that those with high exposure to an adverse risk factor die sooner than those with lower exposure. Therefore the prevalence of such a high exposure in the population will diminish with age, also without any transitions between risk factor classes taking place. This effect can be taken into account by using the relative risks on death to calculate the amount of selection.

This implies that when no relative risk on death is specified in the simulation configuration screen, net transition rates are calculated without taking selective mortality into account.

Relative risks on death equal to 1 versus no relative risk on death

With relative risks for diseases, not specifying a relative risk on this disease (on the relative risk tab of the model configuration screen) implies that these relative risks are assumed to be 1. A relative risk of 1 implies that there is no effect of the risk factor on the incidence of this disease, that is, the incidence is the same in all risk factor groups. Specifying a relative risk of 1 therefore will give the same result as not specifying a relative risk.

The same, however, is not true for relative risk of death. When a relative risk of death of 1 is specified, the relative risk for other cause mortality in the model is calculated in such a way that no overall effect of the risk factor on initial total mortality is seen. Initial total mortality is the total mortality at the start of the reference simulation. So if there are diseases in the model which increase mortality in e.g. higher exposure groups, the other

cause mortality in these groups will be lowered in order to produce the same total mortality in both groups. A relative risk of 1 thus forces a calculation of relative risks for other cause mortality that compensate any mortality effects of diseases.

When no relative risk on death is specified, the relative risk on other mortality is made 1, thus not the relative risk on total mortality. This means that if there are diseases in the model which increase mortality in e.g. higher exposure groups, the total mortality in these groups will also be higher. All exposure groups have the same other mortality, so differences in total mortality are driven by differences in the prevalence of disease.

Odds ratios for disability equal to 1 versus no Odds ratios

Similar to user RR of 1 for mortality, when specifying Odds ratios of 1, DYNAMO-HIA forces that the impact of the risk factors on disability is entirely through the modeled diseases. This implies that other disability is adapted to ensure that OR is 1.

Relative risks on death when using continuous risk factors.

Apart from the effect on net transitions, relative risks on death are used to estimate a relative risk on other cause mortality. For categorical risk factors this can usually be done exactly. The exception is when total mortality as given to the program is so close to the sum of all mortality related to diseases (also as given to the program) that the other cause mortality (the difference between total mortality and disease related mortality) becomes negative in some risk groups.

For continuous risk factors, first other mortality is calculated for a large range of values of the continuous risk factor. Second an exponential function is fitted, giving other cause mortality as an exponential function of risk factor level. The relative risks on death determine how quickly total mortality rises with risk factor level. This is also an

exponential function. In practice it can happen that disease related mortality increases more quickly with risk factor level than total mortality. In that case other cause mortality (the difference between the two) will decrease with risk factor level. That can give strange results in simulations, where a decrease in a deleterious risk factor can lead to more mortality. This is an artifact of the assumed exponential relationship. For continuous risk factors we therefore advise either not to include relative risks on death, or to check in the parameter file “relative relativeRisk_OtherMort” whether the relative risks are (mostly) in the expected direction.

A similar effect can also occur for compound risk factors, but as the effect of forcing a particular shape on the relation between duration of exposure and other mortality are limited to those in the “duration class”, effects will be less severe.

Other cause mortality and compound risk factors

For compound risk factors, the relative risks on other cause mortality in the duration class are fitted assuming an exponential decline, starting at “RRbegin”, and decline towards “RRend”. RRbegin and RREnd are derived differently depending on the values of the RRbegin and RREnd that are given by the user for total mortality.

When the user specifies an RRbegin for total mortality that is equal to the relative risk in a “non-duration” class of the risk factor, RRbegin of other cause mortality is also made equal to the relative risk of other cause mortality in that same class. Similarly, when the user specifies an RREnd for total mortality that is equal to the relative risk in a “non-duration” class of the risk factor, RREnd of other cause mortality is also made equal to the relative risk of other cause mortality in that same class. Only when it proves impossible to fit the required curve, these restrictions are dropped.

After fitting this relative risk curve, the other mortality figures are calibrated so that the average mortality in the initial reference population is equal to the total mortality specified by the user. If the fitted values for other cause mortality in the duration class are very from the values that they were fitted on, this also changes the mortality in “non-duration” classes, sometimes importantly so.

The user therefore is advised to check the fitted other cause mortality, as written to the file `otherMortData.csv` (see page 58). One possible solution for improving the fit of the other cause mortality is to lift the restrictions on `RRbegin` or `RRend`. This can be done by changing the input `RRbegin` and/or `RRend` given for total mortality a little bit, so that they are not exactly the same as the relative risks given for one of the other classes.

Comparing input and output incidence

The incidence calculated by DYNAMO as output is the cumulative incidence in one year in the entire population. This means that the nominator of the output incidence is the number of new cases getting the disease during the simulated year (including those that die shortly after). The denominator is the entire population at the start of the simulated year, thus **including** persons that already have the disease. In contrast, the incidence rate that is input for the program is the incidence rate as is usually determined by epidemiological studies: Input incidence rate should be the instantaneous transition rate to disease in those without the disease, thus the rate of newly getting the disease in disease free individuals. In that case the denominator consists only of disease-free individuals. This implies that the output incidence will usually be smaller than the input incidence rate.

Appendices

Appendix A. System Requirements

The system on which the DYNAMO-HIA application is going to be installed is restricted to the minimum requirements described below.

In the table below the minimum system requirements for installation of the DYNAMO-HIA application on a Windows system are described. Depending on the number of risk factor classes, the number of diseases and the type of scenario that is run, DYNAMO-HIA can be memory greedy.

Item	Minimum Requirements
Operating System:	XP (with .NET Framework 3.5 SP1 installed)
Computer Processor:	2,2 Ghz AMD Athlon 64 X2 Dual Core or better (e.g. Intel)
Computer Memory:	3,00 GB of RAM
Screen Resolution:	1024x768

Appendix B: Recommended Naming Conventions

DYNAMO allows storing and using a large number of files in a single work directory, such as several different incidence files for the same disease. This might occur when having several different populations in the work directory or different incidence data for the same disease to, say, conduct a sensitivity analysis. The xml files within DYNAMO, however, do not carry any additional information about content and origin beyond the name of the file. Hence, we suggest a naming scheme for the created xml-files which could be used within DYNAMO. This naming scheme is not necessary to use DYNAMO and every user is welcome to adjust the scheme to his own needs or devise a completely new one for his use.

This naming scheme classifies the data first by country and then in the three groups of reference data: population, disease, risk factor and in addition the group relative risk, which is assumed to be the same for all countries/regions. Next the actual name is given (either risk factor name or disease name), in the case of risk factors one should consider to include information on the measurement level as one, say, could model BMI with 3 categories or 5 or even more. Finally the characteristics should be included. This naming scheme allows for a distinctive naming of each file and allows ordering them in a file browser in such a way that related data are next to each other.

*Table 1: Suggested Naming Conventions for XML files***Population**

<u>Country/Region</u>	<u>DataSection</u>	<u>Attribute</u>
<i>e.g. UK</i>	<i>Pop</i>	<i>Size</i> <i>Newborns</i> <i>Overalldisability</i> <i>OverallMort</i>

Example:

UK_Pop_Size

UK_Pop_OverallDALY

Risk Factor

<u>Country/Region</u>	<u>DataSection</u>	<u>Name</u>	<u>Measurement Type incl. # of classes</u>	<u>Attribute</u>
<i>e.g. UK</i>	<i>RF</i>	<i>e.g. BMI</i>	<i>{cat10, cont, Duration}</i> <i>{Zero, Net, UserSpec}</i>	<i>Prevalence</i> <i>Transition</i> <i>In case of compounding RF split up in {Distribution, Prevalence}</i>

Example: UK_RF_BMI_cat5_Prevalence

Disease

<u>Country/Region</u>	<u>DataSection</u>	<u>Name</u>	<u>Attribute</u>
<i>e.g. NL</i>	<i>Disease</i>	<i>e.g. Stroke</i>	<i>Disabilty</i> <i>ExcMort</i> <i>Inc</i> <i>Prev</i>

Example: UK_Disease_Diabetes_ExecMort

Relative Risk

<u>Data Section</u>	<u>Source</u>	<u>Target</u>
<i>RR</i>	<i>Riskfactor name</i>	<i>Disease</i>
	<i>Disease name</i>	<i>Death</i>
		<i>Disability</i>

Example:

RR_BMI_cat5_Diabetes

Appendix C. List of ERROR and WARNING messages

In this section we give a list of the known “Error” and “Warning” messages that might appear when running or installing DYNAMO. We do this to give additional information why the error might occur and how severely the warning might affect the model outcome. In many cases an error might indicate inconsistencies in the input data.

Errors reading files

Reading error encountered when reading file: [FileName] with message: “[...]”.

This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that caused the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

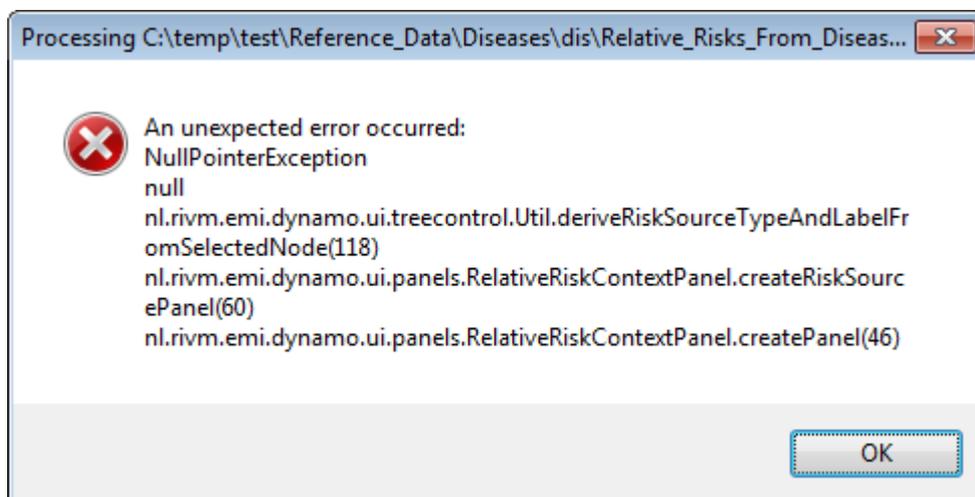
Disease DISEASENAME is related to another disease and has a cured fraction. This combination is not allowed. Please change this .

The DYNAMO-HIA model does not allow relations between diseases with a cured fraction and other diseases. So no relative risks of diseases on other diseases can be specified where one of those diseases has a cured fraction. To run the model after this

warning, remove (in the relative risks tab of configuration screen) the disease-on-disease relative risks pertaining to the disease named.

Disease DISEASENAME is both a cause of another disease and is caused itself by another disease. This combination is not allowed. Please change this .

The DYNAMO-HIA model allow only a single “causal” layer of intermediate diseases. So if there is a relative risk specified for diabetes on IHD, it is not possible to include also a relative risk of IHD on stroke. It is possible, however, to have both a relative risk of diabetes on IHD and a relative risk of diabetes on stroke. In the example, one needs to remove (in the relative risks tab of configuration screen) either the relative risk of diabetes on IHD, or that of IHD on stroke.



This error can occur when opening a file containing relative risks for disease-on-disease. It occurs when the causal disease is not (completely) present in the reference data. This can happen when this file was copied into the directory rather than imported with the DYNAMO-HIA interface, or when the causal disease (or one of its subfiles, like the excess mortality file) is deleted after importing this file.

Errors generated by the parameter estimation module

Mortality from Case Fatality is larger than total mortality for age [a] and gender[s] and riskgroup [r].

Program will not run unless this problem is solved first.

Please change the input

In risk group r the total case-fatality, i.e. incidence times acutely fatal fraction for all diseases together, is larger than total mortality. This can be caused by high values of incidence and case-fatality, but also by extremely low relative risks for all cause mortality and might indicate inconsistent input data.

negative attributable mortality estimated after 10 iterations!!

Message given for age [a] and gender[s].

Most common reason is that the mortality from acutely fatal disease is larger than excess mortality

After adjustment for mortality due to other causes than the disease, the excess mortality from the disease becomes negative. See technical report “detailed model specification, section **3.3.3**.

FATAL ERROR: Attributable Mortality from diseases exceeds the overall mortality for age [a] and sex[s]

Please lower excess mortality rates or case fatality rates or disease prevalence rates, or increase total mortality rate

The excess mortality from all diseases and from acutely fatal diseases combined is higher than the total mortality in the population. This might indicate inconsistent input data. See technical report “detailed model specification, section **3.3.4**

Regression for other mortality failed. Average RR for the durationclass is [X] for age [a] and sex [s].

This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message

The RR for other mortality is put to [X] for all durations. Note that incidence of diseases is still duration dependent as specified.

The RRbegin and RREnd for other mortality in the duration class could not be estimated. There the RR for other mortality is assumed to be constant. See technical report detailed model specification, section **3.3.4**

Bug in program when calculating baseline disability odds. Total disability given by user =[X] but calculated from baselineDisabilityOdds [Y];

This messages should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

Regression for other mortality failed

This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

*non-linear regression other cause mortality did not converge in 500 iterations results:
alpha [A] RR end X RR begin [Y] criterium = [C];*

The regression that estimates the relative risk for the duration class of a compound risk factor has failed. This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

ERROR:

*Overall disability is smaller than disability due to diseases for age [a] and gender [s]
: disability due to diseases: [X] and overall:[Y].*

The program will not run. Please provide other input data.

The disability specified for the individual diseases, combined with the prevalence rates specified for these diseases together yield a disability for the population that is higher than the overall disability specified for the entire population. DYNAMO-HIA assumes that the total disability data are the accurate data, and thus no consistent calculations can be carried out. This is similar to the approach for mortality.

Warnings generated by the parameter estimation module:

100% of the initial population has the same duration. Therefore it is not possible to estimate a time dependent other mortality or other disability. In case other mortality/disability is requested, those relative risks will be made constant over time.

See technical report “detailed model specification, section **3.3.4**

median survival rates for age X and sex 0/1 for disease “diseaseName” are inconsistent with the median survival at the next higher age groups. Please check the data and make sure that survival does not decrease abruptly over age.

See calculation document section **3.2.1**

negative other mortality = [xx] for person [i] for riskclass [r] age: a] sex: [s]

For a simulated person in the population on which the parameters are estimated, the other mortality becomes negative. This occurs mostly in case of a continuous risk factor, in those with extreme values of the risk factor.

*negative other mortality in [X] % of simulated cases for age[a] and gender [s].
no more warnings of this kind will be generated for other age and gender groups*

For [X]% of the population for which the parameters are estimated, other mortality becomes negative. This indicates that, at least for some risk factor groups, the effect of the risk factor on mortality through the modeled diseases is larger than it is implied by the relative risk of the risk factor on all-cause mortality. Leaving out the relative risk on all cause mortality would be an option in this situation, as most of the effects of the risk factor in that case is already modeled by the effects through diseases.

WARNING:

the disability from diseases given for riskfactor group XX in age X and sex X is larger than the disability implied by the odds ratio for disability.

Therefore disability for this group will be calculated solely on disease status and not on risk factor status.

For a simulated person in the population on which the parameters are estimated, the ability from risk factor status became larger than 1. Therefore this ability is set to 1, and the odds ratio for disability is not longer reproduced exactly in the simulation. This occurs mostly in case of a continuous risk factor, in those with extreme values of the risk factors.

different baseline mortalities calculated after calibration nl [XX] after calibration while [YY] before (age= [age] ; sex= [sex])

Recalibration of baseline other mortality yields a different number. This is normal for continuous and compound risk factors, but differences should not be extremely large

Excess mortality of disease [XX] is zero for age [a] and gender [sex]

The program assumes a zero attributable mortality for this disease

No more warning messages of this kind are given for other age/gender/disease groups

If excess mortality is zero, in many cases a negative attributable mortality will be calculated, as in case of a zero attributable mortality in those cases a small positive excess mortality would be present, because those with disease have a worse risk factor pattern than those without the disease. DYNAMO-HIA assumes that in this case the user requests a zero attributable mortality instead of a zero excess mortality, and sets the attributable mortality to zero.

See technical report “detailed model specification, section **3.3.4**, under **Estimation in case excess mortality is zero**

100% of the initial population has disability due to at least one disease. Therefore it is not possible to estimate the disability from other (not modelled) diseases. This is made 0 (no disability from other diseases)

This warning is give for age [a]and gender[s] and riskgroup [r]

No more warnings of this kind will be generated for other risk, age and gender groups

All persons in the population have at least one modeled disease and therefore it is not possible to estimate the disability in persons without any disease (as such persons are not present in the population). Persons without any disease (not present at baseline) are all assumed to be perfectly healthy. As it is unlikely that nobody in the population is free of disease, this warning might indicate a inconsistency in the input data.

Errors generated by the simulation

Incidence and mortality data are unrealistically high for cluster [c] containing disease [XX] and risk factor value [Y].

The algorithm used to calculate transitions fails. This mostly occurs because risk factor values (of continuous risk factors) became unrealistically high due to errors in the drift or because of errors in the relative risks given to the model. This might indicate an inconsistency in the input data.



The simulation you are running needs more memory than it allowed to have. See the “Running DYAMO-HIA.exe” item on page 105 for how to increase the amount of memory available as a possible solution for this problem.

Also, a categorical risk factor with a large number of categories (or a continuous one with a large number of cut-offs) require a large amount of memory in scenarios where the initial prevalence is changed but the transitions are the same. Less memory is required when only scenarios are present where also the transitions are changed. If transitions are the same or different is determined based on the name of the transition input file. One can thus trick DYNAMO into thinking transitions are different by copying the transition input file and giving it another name, and using this copy in the scenario. The price for this, however, is that the initial prevalence in the alternative scenario no longer will be exact, but a random draw from the intended prevalence.

Errors generated by the postprocessing module

" not enough simulated information to calculate scenario [X]. No simulated information on changing riskfactor class from[a] into class [b]

DYNAMO simulates a scenario in which only the initial prevalence changes by simulating every person under all possible changes in the scenario. (see section 4.3 of the detailed model specification). This error indicates a problem with reconstructing the scenario population from the separate simulated populations.

This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error

message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

*no simulated individuals with riskclass Name and duration [X] in simulation,
while the prevalence of this riskclass is [xx] for age [a] and gender [s]*

The DYNAMO model does not have any simulated persons in a particular risk class, while there should be such persons as they are present in the “real” population.

This message should not occur when the DYNAMO-HIA model has been used as intended. However, if .xml files have been generated outside the DYNAMO-HIA user-interface, errors made can cause this message. If it occurs in other situations, we would appreciate an E-mail including the file that causes the problem and the full error message to hendriek.boshuizen@rivm.nl, putting “bug in DYNAMO-HIA” in the subject of the message.

Appendix D. Frequently Asked Questions

In this section we give an overview of frequently asked questions from users of DYNAMO.

General

Q: When I click on the names in the explorer tree nothing happens

A: In the DYNAMO program menus appear on *right* clicking only

Running DYNAMO-HIA.exe (on Windows XP or higher)

Q: I want to have some technical background about the software.

A: The DYNAMO-HIA program has been developed using the Java programming language.

Its graphical user interface is based on the Eclipse Rich Client Platform.

WinRun4J has been used to make starting the program easy in Windows and provide icons and JFreeChart has been used for making the output plots.

The software runs on a standard Java Virtual Machine and minimally needs version 1.6 (it is configured to only accept this version). The parameters that are passed to the JVM can be found in the DYNAMO-HIA.ini file that can be found in the same directory as DYNAMO-HIA.exe.

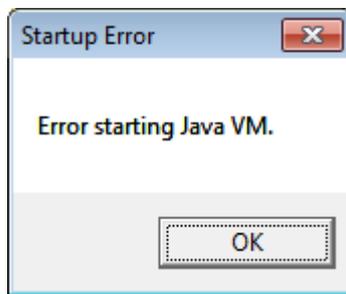
Their lines start with “vmarg.” and they are all about memory:

-Xms128M Means initially 128 Megabytes of memory are made available for the application.

-Xmx1024M Means 1024 Megabytes is the maximum amount the program is allowed to take.

-XX:MaxPermSize=128M Means a certain sort of Java memory may not exceed 128 Megabytes.

When you increase the number behind **-Xmx** too much, however, the following error will appear:



Our experience is that **-Xmx1510M** is the maximum amount allowed on most computers.

When you want to run simulations that need more space than the standard configuration allows you may increase the number after **-Xmx**. Under Windows XP (and higher 32-bit operation systems) the maximum allowed amount of memory is 3 Gigabytes (approx. 3000 Megabytes) and because Windows needs memory as well setting it above 2048M is not a good idea. The amount of physical memory is important. When the amount of required memory exceeds the available physical memory Windows starts making “virtual” memory. This memory space is created by writing the content of a part of the used physical memory to the hard disk and reusing that physical memory. It is nice to have more space, but the price is usually very high: When the content has to be reloaded another part of memory has to be swapped out to hard disk and that process takes orders of magnitude more time than using physical memory. In practical terms: Your

simulation will run extremely slow if its memory use (plus Windows's memory footprint) exceed physical memory.

In 64-bits versions in principle the amount of physical memory that can be used is much higher.

Java heap space

Q: When I run a simulation I get the following popup screen:



A: The simulation you are running needs more memory than it allowed to have. See the “Running DYAMO-HIA.exe” on page 105 item above for how to increase the amount of memory available as a possible solution for this problem.

Reference Data Screens

Q: How can I change the risk factor class which has duration dependent relative risks?

A: You can not change this class anymore. This is because otherwise relative risk files that could already have been entered are not usable anymore. However you can make a new risk factor with another class as the duration class, and import the prevalence and transition rates for this risk factor from the old version of the risk factor.

Simulation Screen

Q: I can not choose a risk factor that I have entered in the reference data

A: Risk factors can only be chosen as they have been completely defined in the reference data section. For risk factors this means that there must be minimally a valid prevalence file and a valid transition file present.

Q: I can not choose a disease that I have entered in the reference data

A: Diseases can only be chosen as they have been completely defined in the reference data section. For disease this means that there must be minimally valid prevalence, incidence, excess mortality and disability files present.

Q: I can not chose the right transition or prevalence file name on the scenario tab

A: The first reason for this might be that model does not allow you to chose both the transition file and the prevalence file to be equal to that on the reference tab. So this
Sometimes version 1.0 does not refresh the dropdown lists

Output screen

Q: On the “change scenario settings” tab I do not see any sliders and buttons to change the scenario

A: These sliders and buttons are only present when one or more an alternative scenario has be requested. When only the “business as usual” (reference) scenario is run, no such buttons are present, as they only apply to alternative scenarios

Q: I do not see the legend of some of the figures

A: The plots in the output windows of DYNAMO-HIA have a fixed size. Maximize the output window. On low resolution screens this might not be sufficient. In that case increase the resolution of the screen to 768 pixels in the vertical direction (e.g. 1048 by 768).

Appendix E: Example R-code for running a probabilistic uncertainty analysis.

```
## This scripts assumes that there is already a directory with
## the simulation to be run (a directory under "Simulations"
## containing a configuration.xml file)
## Also, it assumes that 100 alternative files are available of
## each file that needs to be resampled
## these files should have the same name as the original file,
## but with _no1 _no2 _no3 etc. added to the filename (before
## the .xml, and for RR files, before the -riskfactorname.xml),
## so for instance: RR_CHD_salt-salt.xml will need 100
## additional files named RR_CHD_salt_no1-salt.xml to
## RR_CHD_salt_no100-salt.xml files )

## give the DYNAMO work directory (where the data are)
## NB THIS PATH SHOULD NOT CONTAIN ANY SPACES !!!!!!!

basisWD <-"R:/Projects/DYNAMO_workdirs/Netherlands/"

## NB in the next statement you should use \\ as a directory
## separator and NOT /

## the directory that contains DYNAMOHIA.exe

runDir<-('C:\\DYNAMO-HIA-2 Application\\eclipse - 64bits')

## give the name of the simulation (= name of the existing
## subdirectory of the Directory "simulations" containing the
## configuration.xml file)

name.simulation<-"Nederland_5gram"

## give the part of the filename to which _no1 _no2 etc is added
## NB this should be a unique string, not used in other
## filenames that are used in the simulation (unless they need
## to be changed too)
## or in xml tags as used in configuration.xml

filepart<-"zout_1-2012"
setwd(basisWD)

## read the configuration.xml file
fileName<-
paste("Simulations/",name.simulation,"/","configuration.xml",sep
="")

CONFIGbasis<-readChar(fileName, file.info(fileName)$size)
```

```
## loop over the number of draws of the uncertainty
## parameters
for (iter in 1:100)

{

  setwd(basisWD)
  ## make the simulation directory and write
  ## the configuration.xml file to that directory

  simname<-paste(name.simulation,iter,sep="_")
  fileName<-paste("Simulations/",simname,"/", "configuration.xml",sep="")
  CONFIG <-gsub(filepart,paste(filepart,"_no",iter,sep=""),CONFIGbasis, fixed=T)
  dir.create(paste("Simulations/",simname,sep="") )
  writeChar(CONFIG,fileName,eos=NULL)

  ## make the file needed by the DYNAMO batchrunner
  ## which only contains the simulation name
  writeChar(simname,paste(simname,".txt",sep=""),eos=NULL)

  #calls the aforementioned textfile with absolute directory reference from the
  #Dynamo directory ( place of DYNAMO-hia.exe)
  setwd(runDir)
  system.time(shell(paste("runbatch.bat ",basisWD,simname,".txt",sep="")))
  print(paste("runbatch.bat ", basisWD,simname,".txt",sep=""))

}

## this program will yield a set of 100 subdirectories
## under the "simulations" directory
## in these directories there will be a directory "results"
## which contains the output in batchoutput.csv, cohortLE.csv
## and sullivan.csv
## these can be read in and processed.

## the system.time statement copies the content of the
## runbatch.bat file to the console, and additionally
## any output (info and error messages) generated by
## DYNAMO-HIA
## warnings and some error messages are found in the logging
## (written to the runDir as czm_mono)
```

Appendix F: code of R-functions for writing DYNAMO-HIA files

These functions can be used to write input files for DYNAMO-HIA from R.

We only give functions used for the files that are used in modeling of categorical risk factors. However, the functions are easily adapted for the writing of other files.

Also, no functions are given for writing configuration files (e.g. for a risk factor, or for a simulation), as they rarely need to be written in bulk from scratch.

General inputs of these functions are:

dynamodir: name of the DYNAMO-HIA working directory to which the data should be written

filename: name to give to the file (without the path, and without the .xml)

data: multidimensional array with input data. The final dimensions are always age and gender (except for newborns). The number of dimensions and their meaning are given as comments at the start of each function. In most cases, the dimensions are: 1: risk factor level; 2: gender and 3: age. The numbering always starts at 1, for instance age 0 is stored in dimension 2=1. For excess mortality the first dimension gives the type of data: 1=mortality rate, 2=fatal fraction, 3=cured fraction.

ncat: number of risk factor classes

diseasename: name of the disease

RFname: name of the riskfactor

popdir: name of the population

The last three names are used to make the right directories within the DYNAMO-HIA working directory and put the files there. So these functions automatically put the files at the right place in the DYNAMO directory tree.

Technical note: In a previous version of these functions, the R-package XML was used. However, this package is very slow in constructing XML documents. Therefore we have chosen to a less elegant but faster way to make these files.

```
#####
#                                                                 #
#           general functions needed later                       #
#                                                                 #
#           ALWAYS INCLUDE THESE FUNCTIONS !!!!!               #
#                                                                 #
#####

## first define some general functions needed repeatedly by the other functions

makeXML.age.sex.cat<-function(tag1,tag2,data,ncat)
{
  string<-paste('<?xml version="1.0" ?> <',tag1,">",sep="")
  for (age in 0:95){
    for (sex in 0:1) {
      for (cat in 1:ncat)
        string<-paste(string, "<", tag2,"> <age> ",as.character(age), "</age>",
                      " <sex>",as.character(sex),"</sex>",
                      " <cat>",as.character(cat), "</cat>",
                      " <value>",as.character(data[cat,sex+1,age+1]), "</value>",
                      "</",tag2, ">",sep="")
    }
  }
  string<-paste(string, "</", tag1,">",sep="")
  return(string)
}
makeXML.age.sex.cat2<-function(tag1,tag2,data,ncat)
{
  string<-paste('<?xml version="1.0" ?> <',tag1,">",sep="")
  for (age in 0:95){
    for (sex in 0:1) {
      for (cat in 1:ncat)
        string<-paste(string, "<", tag2,"> <age> ",as.character(age), "</age>",
                      " <sex> ",as.character(sex), "</sex>",
                      " <cat> ",as.character(cat), "</cat>",
                      " <percent> ",as.character(data[cat,sex+1,age+1]), "</percent>",
                      "</",tag2, ">",sep="")
    }
  }
  string<-paste(string, "</", tag1,">",sep="")
  return(string)
}

makeXML.age.sex<-function(tag1,tag2,data)
{
  string<-paste('<?xml version="1.0" ?> <',tag1,">",sep="")
  for (age in 0:95){
    for (sex in 0:1) {
```

```

        string<-paste(string, "<", tag2, "> <age> ", as.character(age), "</age>",
                    " <sex>", as.character(sex), "</sex>",
                    " <value>", as.character(data[sex+1,age+1]), "</value>",
                    "</", tag2, ">", sep="")
    }}
    string<-paste(string, "</", tag1, ">", sep="")
    return(string)
}

makeXML.age.sex2<-function(tag1,tag2,data)
{
  string<-paste('<?xml version="1.0" ?> <', tag1, ">", sep="")
  for (age in 0:95){
    for (sex in 0:1) {

      string<-paste(string, "<", tag2, "> <age> ", as.character(age), "</age>",
                    " <sex>", as.character(sex), "</sex>",
                    " <percent>", as.character(data[sex+1,age+1]), "</percent>",
                    "</", tag2, ">", sep="")
    }}
    string<-paste(string, "</", tag1, ">", sep="")
    return(string)
}

makeXML.age.sex3<-function(tag1,tag2,data)
{
  string<-paste('<?xml version="1.0" ?> <', tag1, ">", sep="")
  for (age in 0:95){
    for (sex in 0:1) {

      string<-paste(string, "<", tag2, "> <age> ", as.character(age), "</age>",
                    " <sex>", as.character(sex), "</sex>",
                    " <number>", as.character(data[sex+1,age+1]), "</number>",
                    "</", tag2, ">", sep="")
    }}
    string<-paste(string, "</", tag1, ">", sep="")
    return(string)
}

#####
#
#                               XML writing functions                               #
#
#####

##### function to write #####
##### risk factor prevalence #####

## data: 3-dimensional array of dimension=c(ncat,96,2)
## dimension 1: risk factor level
## dimension 2: gender (1 = men, 2 = women)
## dimension 3: age (1 = 0 year, 2 = 1 year ... 96 = 95+ year)

writeRiskFactorsPrev<-function(RFname, ncat, dynamodir, filename , data)
{
  outdirDP<-paste(dynamodir, "/Reference_Data/Risk_Factors/", RFname,
                  "/Prevalences", "/", sep="")
  outfilename<-paste(outdirDP, filename, ".xml" , sep="")
  outfilename<-gsub(" ", "_", outfilename)
  # write data

  dynamo<-makeXML.age.sex.cat2("riskfactorprevalences_categorical", "prevalence", data, ncat)

  if (!file.exists(outdirDP)) dir.create(outdirDP, recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

```

```
##### function to write RR for a #####
##### categorical riskfactor on disease #####

## data: 3-dimensional array of dimension=c(ncat,2,96)
## dimension 1: risk factor level
## dimension 2: gender (1 = men, 2 = women)
## dimension 3: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeRRriskfactorCat <-
function(diseasename, riskfactorname, ncat, dynamodir, filename , data)
{
  outdirDP<-paste(dynamodir,"/Reference_Data/Diseases/",diseasename,
                  "/Relative_Risks_From_Risk_Factor","/", sep="")

  outfilename<-paste(outdirDP,filename,"-",riskfactorname,".xml" , sep="")
  ## outfilename<-gsub(" ", "", outfilename)
  ## outfilename<-gsub("no.", "no", outfilename)

  # write data

  dynamo<-makeXML.age.sex.cat("relrisksfromriskfactor_categorical","relativerisk",data,ncat)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
  ## print(paste(outfilename, "written"))
}

##### function to write RR for a #####
##### riskfactor on all cause mortality #####

## data: 3-dimensional array of dimension=c(ncat,2,96)
## dimension 1: risk factor level
## dimension 2: gender (1 = men, 2 = women)
## dimension 3: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeRRMortality<-function(RFname, ncat, dynamodir, filename , data)
{
  outdirRRD<-paste(dynamodir,"/Reference_Data/Risk_Factors/",RFname,
                  "/Relative_Risks_For_Death","/", sep="")
  outfilename<-paste(outdirRRD,filename,".xml" , sep="")
  outfilename<-gsub(" ","_", outfilename)
  # write data
  dynamo<-makeXML.age.sex.cat("relrisksfordeath_categorical","relriskfordeath",data,ncat)

  if (!file.exists(outdirRRD)) dir.create(outdirRRD,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

##### function to write the odds ratio for a #####
##### riskfactor on all cause disability #####

## data: 3-dimensional array of dimension=c(ncat,2,96)
## dimension 1: risk factor level
## dimension 2: gender (1 = men, 2 = women)
## dimension 3: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeORdisability<-function(RFname, ncat, dynamodir, filename , data)
```

```

{
  outdirRRD<-paste(dynamodir,"/Reference_Data/Risk_Factors/",RFname,
                  "/Odds_Ratios_For_Disability","/", sep="")
  outfilename<-paste(outdirRRD,filename,".xml" , sep="")
  outfilename<-gsub(" ","_", outfilename)
  # write data
  dynamo<-
makeXML.age.sex.cat("relrisksfordisability_categorical","relriskfordisability",data,ncat)

  if (!file.exists(outdirRRD)) dir.create(outdirRRD,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

#####
##### function to write disease prevalence #####
#####

## in input array "data" has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeDisPrev<-function(diseasename, dynamodir, filename , data)
{
  filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"/Reference_Data/Diseases/",diseasename,
                  "/Prevalences","/", sep="")
  outfilename<-paste(outdirDP,filename,".xml" , sep="")

  if (!file.exists(outfilename)) file.create(outfilename)

  # write data
  dynamo<-makeXML.age.sex2("diseaseprevalences","prevalence",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

#####
##### function to write disease incidence #####
#####

## in input array "data" has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeDisInci<-function(diseasename, dynamodir, filename , data)
{
  filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Diseases\\",diseasename,
                  "\\Incidences","\\", sep="")
  outfilename<-paste(outdirDP,filename,".xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex("diseaseincidences","incidence",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

#####
##### function to write #####
##### disease Excess mortality #####

## the order of data is as in the DYNAMO interface:

```

```

## male EM, AcFat, CuredF , female EM, AcFat, CuredF
## type is "Rate" or "Median Survival"
## the array data is of dimension c(3,2,96)
## dimension 1: data type (1=EM, 2=percentage Acutely Fatal, 3= CuredFraction)
## dimension 2: gender (1 = men, 2 = women)
## dimension 3: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeExcessMort<-function(diseasename, dynamodir, filename , data, type="Rate")
{
  filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Diseases\\",diseasename,
                 "\\Excess_Mortalities","\\", sep="")
  outfilename<-paste(outdirDP,filename,".xml" , sep="")

  # write data

  ## the information after tag "parametertype" is not read by dynamo so it does not matter
  ## what is given here

  dynamo<- paste('<?xml version="1.0" ?> <excessmortality>',
                 "<unittype>",type,"</unittype>",
                 "<parametertype>Acutely Fatal</parametertype>",
                 "<mortalities>", sep="")

  for (age in 0:95){
    for (sex in 0:1) {
      dynamo<-paste(dynamo, "<mortality>",
                    "<age>", as.character(age), "</age>",
                    "<sex>", as.character(sex),"</sex>",
                    "<unit>",as.character(data[1,sex+1,age+1]),"</unit>",
                    "<acutelyfatal>",as.character(data[2,sex+1,age+1]),"</acutelyfatal>",
                    "<curedfraction>",as.character(data[3,sex+1, age+1]),"</curedfraction>",
                    "</mortality>","\n",sep="")
    }
  }
  dynamo<-paste(dynamo, "</mortalities></excessmortality>",sep="")

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

##### function to write #####
##### disease DALY-weight #####
##### this delivers DYNAMO-1 data #####

## in input array "data" has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeDisDaly<-function(diseasename, dynamodir, filename , data)
{
  filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Diseases\\",diseasename,
                 "\\DALY_Weights","\\", sep="")
  outfilename<-paste(outdirDP,filename,".xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex2("dalyweights","weight",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )

}

##### function to write #####
##### disease disability #####
##### this delivers DYNAMO-2 data #####

## in input array "data" has the following dimensions:

```

```

## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeDiseaseDisability<-function(diseasename, dynamodir, filename , data)
{
  filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Diseases\\",diseasename,
                  "\\Disability","\\", sep="")
  outfilename<-paste(outdirDP,filename,".xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex2("dalyweights","weight",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )

}

##### function to write #####
##### RR disease on disease #####

## in input array "data" has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeRRdisease <-
function(diseasename, causaldiseasename, dynamodir, filename , data)
{ filename<-gsub(" ","_", filename)
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Diseases\\",diseasename,
                  "\\Relative_Risks_From_Diseases","\\", sep="")
  outfilename<-paste(outdirDP,filename,"-",causaldiseasename,".xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex("relrisksfromdisease","relativerisk",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)

  cat(dynamo, file = outfilename, sep = "\n" )

}

##### function to write #####
##### population size #####

## in input array "data" has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeSize<-function(dynamodir, popdir, data)
{
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Populations\\",popdir,"\\",sep="")
  outfilename<-paste(outdirDP,"size.xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex3("populationsize","size",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )

}

##### function to write #####
##### newborns #####

```

```
## the input data is a vector (one dimensional array) containing the newborn data starting in the
year "startingyear"
## only the first 30 elements are used. If it is short than 30, the other elements up to
## 30 are filled with the last value of the vector
```

```
writeNewborn<-function(dynamodir, popdir, sexratio, startingyear, data)
{
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Populations\\",popdir,"\\",sep="")
  outfilename<-paste(outdirDP,"newborns.xml" , sep="")

  # write data

  maxdata<- length(data)

  dynamo<-'<?xml version="1.0" ?> <newborns>'
  dynamo<-paste(dynamo,"<sexratio>", as.character(sexratio),"</sexratio>",
                "<startingYear>", as.character(startingyear) ,"</startingYear>", " <amounts>",
                sep="")
  for (year in 0:29){

    dynamo<-paste(dynamo, "<amount> <year> ",as.character(startingyear+year), "</year>",
                  sep="")
    if (year< maxdata) dynamo<-paste(dynamo,"
<number>",as.character(round(data[year+1])), "</number>",
                  sep="") else
      dynamo<-paste(dynamo, " <number>",as.character(round(data[maxdata])),
                    sep="")
    dynamo<-paste(dynamo,"</amount>",sep="")
  }

  dynamo<-paste(dynamo,"</amounts>","</newborns>",sep="")

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

```

```
##### function to write #####
##### total mortality #####
```

```
## in input data files has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)
```

```
writeMortality<-function(dynamodir, popdir, data)
{
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Populations\\",popdir,"\\",sep="")
  outfilename<-paste(outdirDP,"overallmortality.xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex("overallmortality","mortality",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}

```

```
##### function to write #####
##### total disability #####
```

```
## in input data files has the following dimensions:
## dimension 1: gender (1 = men, 2 = women)
## dimension 2: age (1 = 0 year, 2 = 1 year .... 96 = 95+ year)

writeOverallDisability<-function(dynamodir, popdir, data)
{
  outdirDP<-paste(dynamodir,"\\Reference_Data\\Populations\\",popdir,"\\",sep="")
  outfilename<-paste(outdirDP,"overalldisability.xml" , sep="")

  # write data
  dynamo<-makeXML.age.sex2("overalldisability","weight",data)

  if (!file.exists(outdirDP)) dir.create(outdirDP,recursive = TRUE)
  cat(dynamo, file = outfilename, sep = "\n" )
}
```