FRESHER

FORESIGHT AND MODELLING FOR EUROPEAN HEALTH POLICY AND REGULATION

D 5.3
Scientific paper on the methodology, results and recommendation for future research

Report Information

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Project Information

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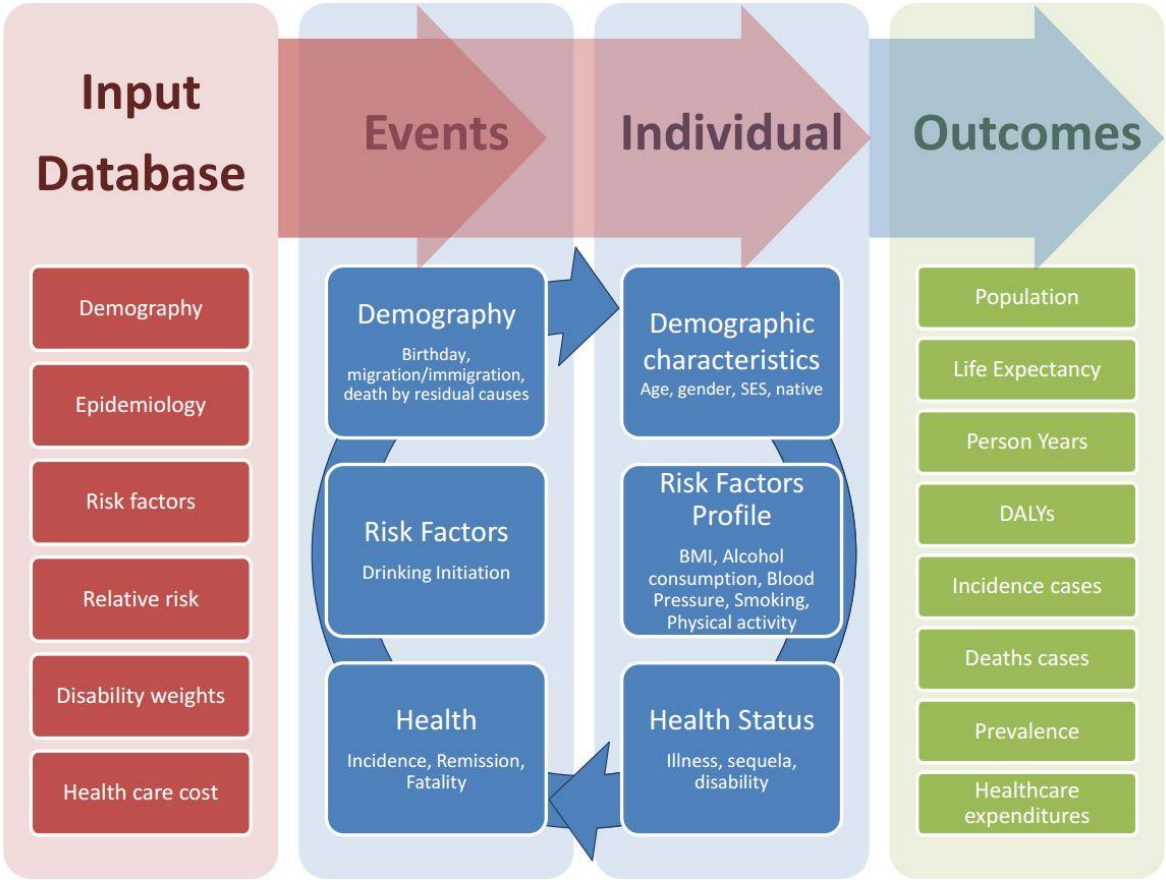
1. Microsimulation principles

1.1. Main principles

The FRESHER microsimulation model is designed to model the impacts of behavioural and metabolic risk factors on chronic diseases and longevity, as well as the extent to which specific policies can modify those impacts.

The model uses case-based microsimulation to create representative synthetic life histories from birth to death providing multiple cross-sectional representations of a population during the 'validation period' – when both simulated and historical data are available and can be compared to validate or calibrate the model (1990-2015) – and the 'projection period' – over which quantitative estimates of the future global burden of chronic non-communicable diseases (NCDs) in the EU and policy impact (2016-2030 and 2016-2050) are simulated.

Figure 1.1 Microsimulation model



1.1.1. Continuous time event based model

The model simulates life histories in continuous time. An individual is described with a set of different characteristics modelling relevant dimensions for public health –demography, risk factors, health.

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A set of events is attached to the individual –birthday, immigration, migration, death, drinking initiation, incidence, remission and fatality. In most cases, time to event is stochastically determined based on a distribution function of individual characteristics.

Those events s compete with each other, i.e. the shortest time to event will determine what event happens first. An event can modify individual characteristics and consequently impact the likelihood of other events occurring (by modifying the intensity of their distributions). Once the individual is initialized, it is then simulated from birth to death though this competing event mechanism.

1.1.2. A synthetic population

The model creates representative synthetic life histories from birth to death providing a cross-sectional representation of the population during the validation (1990-2015) and the projection period (2016-2050). During the validation period both the simulated population and the historical one are available and can be compared to assess the ability of the model to coherently reproduce the cross-sectional distribution of the population.

Due to memory issue, it is not possible to record the entire life of every simulated individual. The model produces aggregated tables. Those tables can record:

- The number of individual with certain characteristic (e.g. alive for the population table and disease status for the disease prevalence table)
- The number of events occurred during the last year (e.g. deaths events and disease incidence events)
- Cumulative outcomes per year: (e.g. health expenditures and DALYs)

Those tables are then rescaled to provide cross-sectional estimates of the population. During the validation period both the simulated population and the historical one are available and can be compared to assess the ability of the model to coherently reproduce the cross-sectional distribution of the population.

More details are available in Deliverable 5.1.

1.2. Modelling uncertainty

1.2.1. Simulation uncertainty

To estimate the simulation uncertainty, we distribute the simulation into subsamples (for example 20). For every outcome, we record the table for all the subsamples. This allows us to compute the mean, and the standard deviation of every outcome.

1.2.2. Baseline uncertainty

The uncertainty of the baseline comes from the uncertainty of the input parameters. For the FRESHER project we do not include that uncertainty in our modelling. It means we are running the model with the mid estimate for every parameter.

1.2.3. Scenario/Intervention uncertainty

The main purpose of the model is to assess the impacts of an alternative scenario, or of an intervention, on the outcomes. To do so we run the model twice (with the same seed) and we compare the outcomes. As we can distribute the simulation into subsamples we can compute the difference between the baseline

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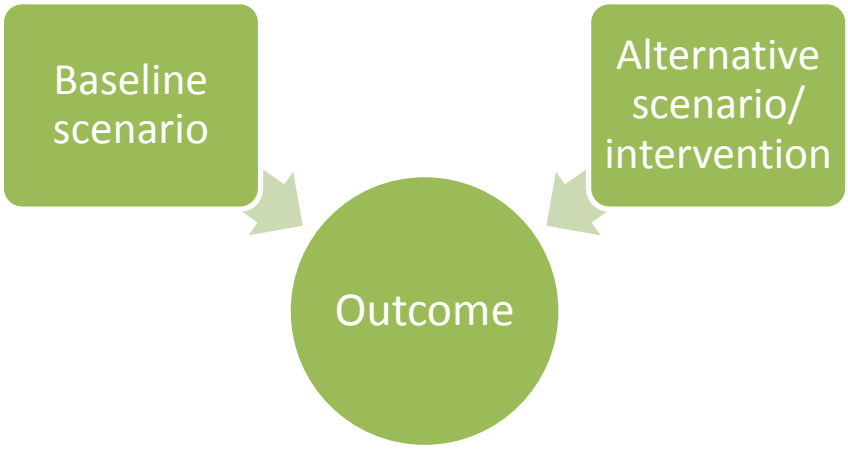
and the alternative scenario for each subsample and then compute the standard deviation of the difference.
We are making the hypothesis that most of the uncertainty on the baseline "disappeared" when we compute the delta and by consequences that the mean and the standard deviation of the delta outcomes represent the true uncertainty of the scenarios differences.



1.2.3.1. Intervention uncertainty

Most of the uncertainty comes from the uncertainty on the intervention's parameters. The model can estimate this uncertainty by running the intervention with different set of parameters and then provide different estimates for the outcomes. This has not been done for the moment, in the FRESHER results.

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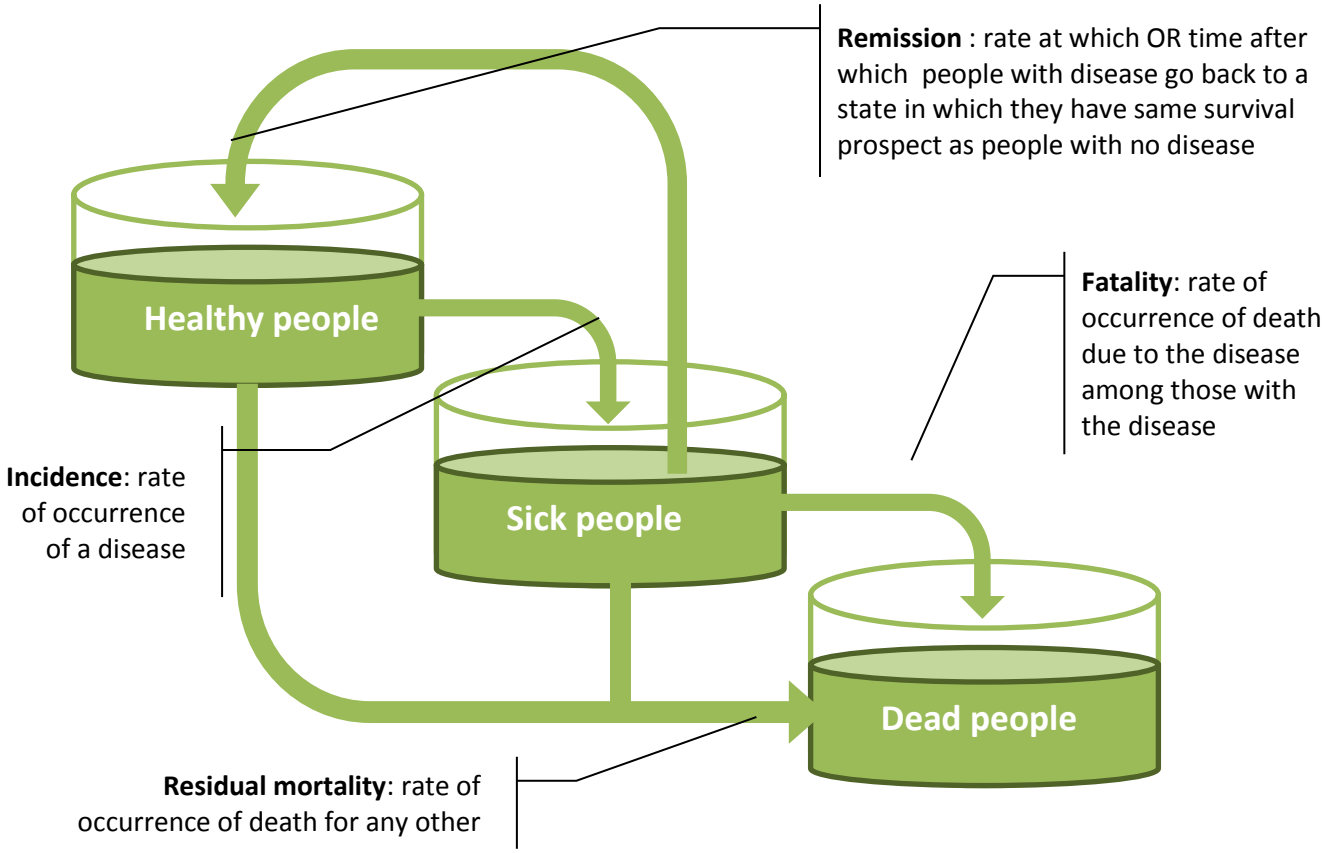
2. Diseases

2.1. Standard diseases

We are basing our modelling on the epidemiological estimates from the GBD 2015 project. The majority of diseases and injuries are modelled using DisMod-MR 2.0, a Bayesian mixed-effects meta-regression modelling tool developed for GBD analyses. This tool provides estimates for incidence, remission, fatality and prevalence rate for over 300 conditions in 195 countries and territories from 1990 to 2015. We have accessed to the data through the web tool Epi Visualization | IHME Viz ((IHME))

2.1.1. Model

Figure 2.1: Modelled disease pathway



The IHME dataset gives us access to incidence, fatality, remission rate for every disease. We model the disease pathway described in Figure 2.1, through 3 events –incidence, remission, and fatality. The remission and the fatality hazard ratio are directly derived from IHME database. As risk factors impact disease incidence, we multiply the baseline incidence by a factor taking into account the risk profile of the individual as explained in 3.1.2.

For certain diseases –stroke, myocardial infarction, injuries – even if the individual experienced remission, it keeps a "sequela" which can impact its quality of life and the incidence of other events.

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2.2. Cancers

2.2.1. Available data:

In the IHME framework, cancers are not modelled with DismodMR-2. We are the using two other data sources:

- **IHME GDB 2015 Result Tools**. In this web tool we have access to the incidence and death rate for most of cancers by gender, age-group from 1990 to 2015.
- **GLOBOCAN IARC**. In those data also available online, we are using the total incidence, plus the prevalence at 1 (resp. 3 and 5) year, i.e. the total number of people living with a cancer diagnosed less than one (resp. 3 and 5) years ago.

2.2.2. Modelling

To model cancers, we assume that cancers duration is 5 year. It means that if the individual does not die within the 5 years it will be considered as fully recovered and will go back to a state in which it have same survival prospect as people with no disease.

We model the cancer pathway with 3 events incidence, remission and death. Once the individual pass through the incidence-event, we determine randomly, based on the survival rate at 5 years (see 2.2.2.2. , if he will die within the 5 years or if he will survive. If he survives the time to the remission event is set at 5Y (and the death event to infinite), if it will dies in the 5Y we set the time of the death event using the distribution of deaths computed below.

2.2.2.1. Distribution of death by cancer

Death by cancer does not occur uniformly within the 5 years of illness, e.g. people die more frequently during the first year. We use the data from IARC to compute the distribution of deaths during the 5 years. We introduce a "survival rate" depending on the year since diagnosis. We then have:

$$P1Y = sr_0 * I$$
$$P3Y = sr_0 I + sr_0 * sr_1 * I + sr_0 sr_1 sr_2 I$$
$$P5Y = sr_0 I + sr_0 sr_1 I + sr_0 sr_1 sr_2 I + sr_0 sr_1 sr_2 sr_3 I + sr_0 sr_1 sr_2 sr_3 sr_4 I$$

We assume that $sr_1 = sr_2$ and $sr_3 = sr_4$, which led us to

$$sr_0 = \frac{I}{P1Y}$$
$$sr_2^2 + sr_2 + 1 = P3Y/P1Y$$
$$sr_4^2 + sr_4 = \frac{P5Y - P3Y}{sr_0 sr_2^2 I}$$

We solve the equations (one unique positive solution) and we can then compute the number of deaths which occurs every year during the cancer duration:

$$Death_{Total} = 1 - sr_0 * sr_1 * sr_2 * sr_3 * sr_4$$
$$Death_i = n_{i-1} * (1 - sr_i)$$
$$n_i = n_{i-1} * sr_i, n_0 = 1$$
$$w_i = Death_i / Death_{Total}$$

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We use the w_i to determine the time of the death event. For example if the weights are (0.5, 0.3, 0.1, 0.07, 0.03) it means that 50% will occur during the first year of disease, 30% during the 2sd year and successively. The date of the death event is computed randomly. From the uniform distribution we pick a quantile; we then convert in time using the distribution of time to death as in Figure 2.3, e.g. 0.25 will convert into a time to death equal to 6 months.

We use the w_i to determine the time of the death event. For example if the computed weights are (0.5, 0.3, 0.1, 0.07, 0.03), it means that 50% will occur during the first year of disease, 30% during the 2sd year and successively. The date of the death event is computed through a random number, e.g. 0.25 will convert into a time to death equal to 6 months.

Figure 2.2: Example of the distribution of time to death for cancers

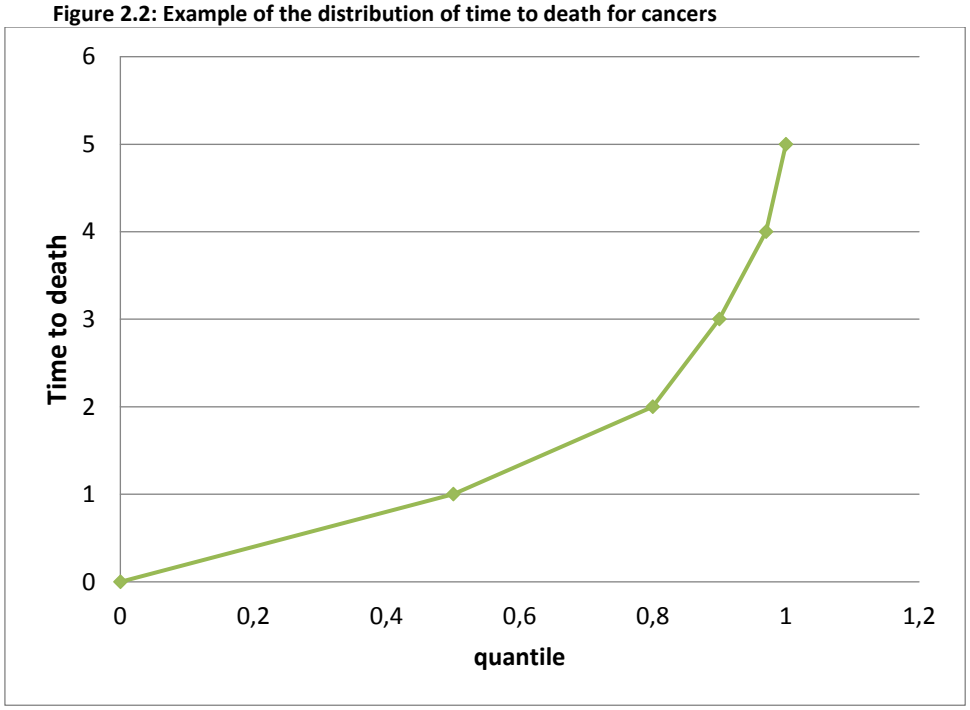

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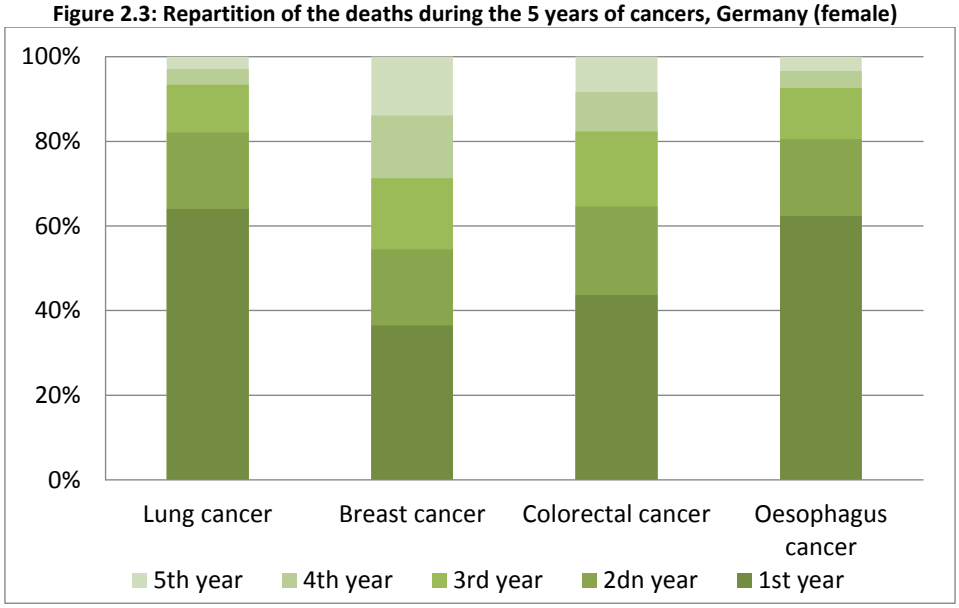
Figure 2.3: Repartition of the deaths during the 5 years of cancers, Germany (female)



2.2.2.2. Survival rate at 5Y

We use incidence and mortality data (from IHME) to compute the survival rates at 5 year (by gender, year and age). The deaths by cancer for a specific year, age depends on the incidence of the past five years, on the survival rates at 5 years and on the distribution of deaths we computed previously.

$$\begin{aligned} d(y,n) = {} & i(y-1,n-1) * sr(y-1,n-1) * w_0 \\ & + i(y-2,n-2) * sr(y-2,n-2) * w_1 \\ & + i(y-3,n-3) * sr(y-3,n-3) * w_2 \\ & + i(y-4,n-4) * sr(y-4,n-4) * w_3 \\ & + i(y-5,n-5) * sr(y-5,n-5) * w_4 \end{aligned}$$

Using a piece-linear function for survival rate where age knots are fixed, we optimize survival rate function to minimize the difference with the input mortality.

Figure 2.4: Survival rate at 5Y, Germany, male, 2015

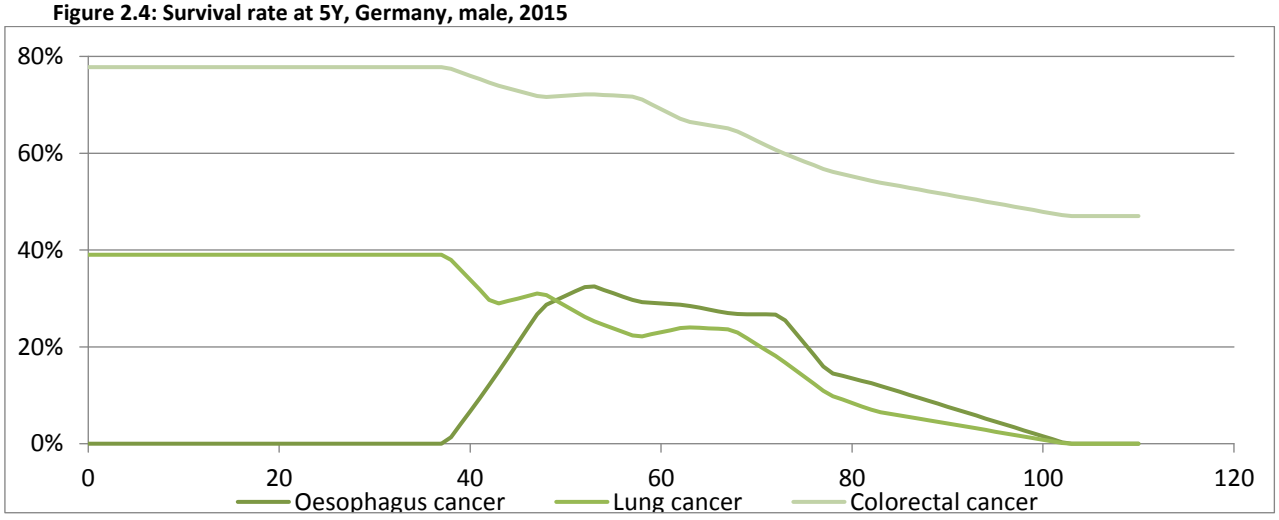


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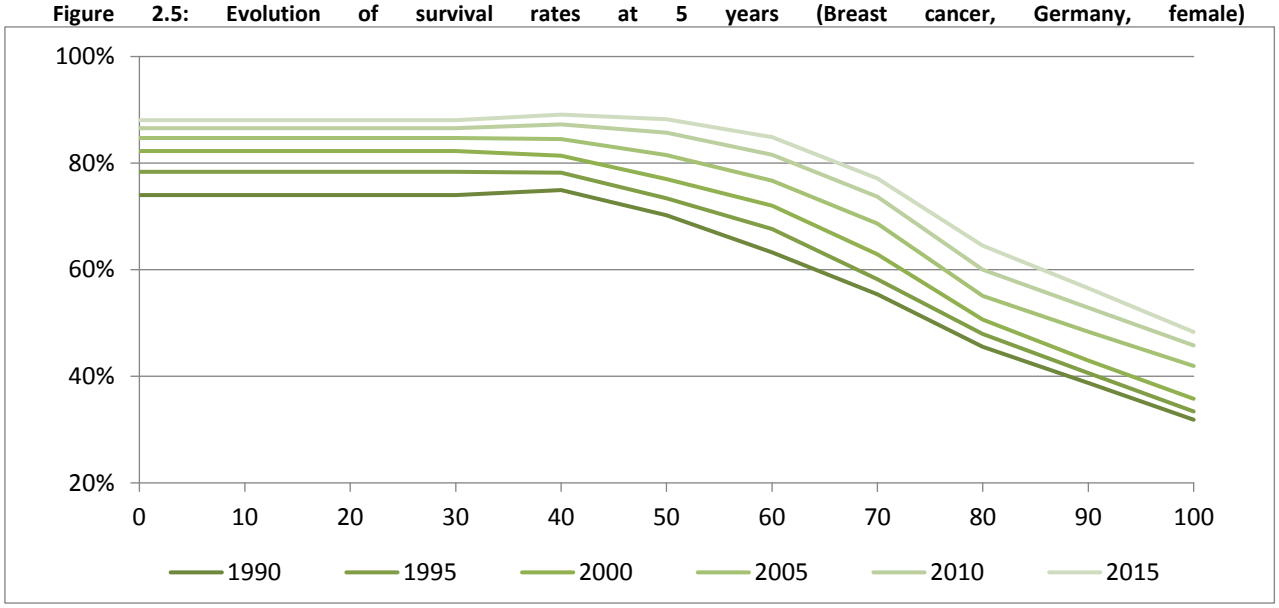
Figure 2.5: Evolution of survival rates at 5 years (Breast cancer, Germany, female)



2.2.2.3. Limitations

There are some limitations in the model. First, when we compute the distribution of deaths, we have only access to one year of data and then we are using the same weights for the entire period. Moreover we don't either have access to age specific data. The distribution of deaths is then assumed to be constant over age.

Nevertheless we manage to calibrate survival rates at five years, and we observe a decrease in the mortality of cancer during the past decades as you can see in Figure 2.5.

2.3. Residual mortality

The cause specific mortality is removed from the total mortality to compute the residual mortality using the following formula:

$$\lambda_r = \lambda - \sum_{i \in disease} P_i \cdot f_i - \sum_{i \in cancers} m_i$$

Where λ (resp. λ_r) is the hazard ratio for the total (resp. residual) mortality, f_i the fatality of disease i (standard IHME diseases) and P_i the prevalence of disease i and m_i the mortality of cancer i .

2.4. Disability weights

We use the methodology described in the technical appendix of the GDB 2015 report on incidence, prevalence and YLDs (Vos et al., 2016[1]) . For each disease they draw a picture of the associated sequelae and health states. They also provided "severity split" we have used to be able to compute an aggregated disability weight for every disease. For each health status we have used the associated disability weight published by WHO in (Mathers et al., 2017[2]). When disability weights were available with and without treatment we have chosen the "with treatment" one.

Every disease is attached to a specific disability weight, the computation of those weights are described in the sections below.

The global disability weight of an individual is then computed every year taking into account it health status during the year. In case of multi comorbidities we use the following formula:

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$$DW = 1 - \sum_i (1 - DW_i)$$

2.4.1. Diabetes

2.4.1.1. Disability weights by severity level

Table 2.1: Disability weight by severity levels for Diabetes

Severity level	Health State	GHE 2015	GBD 2015
Uncomplicated diabetes mellitus	Generic uncomplicated disease: worry and daily medication	0.049	0.049
Diabetic neuropathy	Diabetic neuropathy	0.133	0.133
Diabetic neuropathy with Diabetic foot	Multiple (specific to IHME)		0.02
Diabetic neuropathy with amputation	Amputation of one leg: long term	0.039	0.039
Moderate vision loss due to diabetes mellitus	Distance vision: moderate impairment	0.089	0.031
Severe vision loss due to diabetes mellitus	Distance vision: severe impairment	0.314	0.184
Blindness due to diabetes mellitus	Distance vision: Blindness	0.338	0.187

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.1.2. Methodology

We have used the prevalence of the different sequelae in 2015: "*Diabetic foot", "Amputation due to diabetes mellitus", "Diabetic neuropathy"," Vision impairment due to diabetes mellitus"*, available by country gender and age-group in the IHME dataset. We have used the "with treatment" disability weights for amputation. We have assumed that people only have one sequela and that the difference between 100% and the sum of the available sequelae prevalence represents people with uncomplicated diabetes. We are then able to compute an average disability weights for diabetes by country/year/gender/age-group.

2.4.2. Cerebrovascular Diseases

2.4.2.1. Disability weights by severity level

Table 2.2: Disability weight by severity levels for stroke

Severity level	Health State	GHE 2015	GBD 2015
Stroke, long-term consequences, mild	Stroke, long-term consequences, mild	0.019	0.019
Stroke, long-term consequences, moderate	Stroke, long-term consequences, moderate	0.07	0.07
Stroke, long-term consequences, moderate plus cognition problems	Stroke, long-term consequences, moderate plus cognition problems	0.316	0.316
Stroke, long-term consequences, severe	Stroke, long-term consequences, severe	0.552	0.552
Stroke, long-term consequences, severe plus cognition problems	Stroke, long-term consequences, severe plus cognition problems	0.588	0.588

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.2.2. Methodology

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People who survived a stroke episode are assigned with stroke sequelae for the rest of their life. We are using the mid-level of severity: "Stroke, long-term consequences, moderate plus cognition problems".

2.4.3. Ischaemic heart disease

2.4.3.1. Disability weights by severity level

Table 2.3: Disability weight by severity levels for IHD

Severity level	Health State	GHE 2015	GBD 2015
Acute myocardial infarction, days 1/2	Acute myocardial infarction, days 1-2	0.432	0.432
Acute myocardial infarction, days 3/28	Acute myocardial infarction, days 3-28	0.074	0.074
Mild angina	Angina pectoris: mild	0.033	0.033
Moderate angina	Angina pectoris: moderate	0.08	0.08
Severe angina	Angina pectoris: severe	0.167	0.167

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.3.2. Methodology

See Deliverable 5.1 of the FRESHER project.

2.4.4. Chronic obstructive pulmonary disease

2.4.4.1. Disability weights by severity level

Table 2.4: Disability weight by severity levels for COPD

Severity level	Health State	GHE 2015	GBD 2015
COPD and other chronic respiratory problems, mild	COPD and other chronic respiratory problems, mild	0.019	0.019
COPD and other chronic respiratory problems, moderate	COPD and other chronic respiratory problems, moderate	0.225	0.225
COPD and other chronic respiratory problems, severe	COPD and other chronic respiratory problems, severe	0.408	0.408

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.4.2. Methodology

We have used the prevalence of the different severities of COPD in 2015 available by country gender and age-group in the IHME dataset. And you have computed the average disability weight associated.

2.4.5. Major depressive disorder

2.4.5.1. Disability weights by severity level

Table 2.5: Disability weight by severity levels for major depressive disorder

Severity level	Health State	GHE 2015	GBD 2015	Severity Distribution

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Asymptomatic				13%, 10%-17%
Mild	Major Depressive disorder: mild episode	0.145	0.145	59%, 49%-69%
Moderate	Major Depressive disorder: moderate episode	0.396	0.396	17%, 13%-22%
Severe	Major Depressive disorder: severe episode	0.658	0.658	10%, 3%-20%

Source: IHME-GBD 2015 and WHO-GHE 2015

"To determine the proportion of people with MDD within each of the severity levels, the US National Epidemiological Survey on Alcohol and Related Conditions (NESARC, conducted in two waves from 2001-2002 and 2004-2005) 9 and the Australian National Survey of Mental Health and Wellbeing of Adults (NSMHWB, conducted in 1997) 10 were used to estimate the proportion of MDD cases asymptomatic (13%, 10%-17%), mild (59%, 49%-69%), moderate (17%, 13%-22%), and severe (10%, 3%-20%)."

2.4.5.2. Methodology

Using the severity split and the associated disability weights we have computed an average disability weight for major depressive disorder: DW = 0.219

2.4.6. Alzheimer disease and other dementias

Table 2.6: Disability weight by severity levels for dementia

Severity level	Health State	GHE 2015	GBD 2015	Severity Distribution (by age)		
				<70	70-80	80+
Mild	Dementia: mild	0.165	0.069	79% (71-86%)	71% (63-78%)	61% (53-68%)
Moderate	Dementia: moderate	0.388	0.377	17% (11-23%)	19% (14-24%)	26% (22-30%)
Severe	Dementia: severe	0.545	0.449	4% (2-7%)	9% (5-13%)	12% (7-17%)

Source: IHME-GBD 2015 and WHO-GHE 2015

"In GBD 2013 (and used in GBD 2015), we extracted data from studies reporting on mild, moderate, and severe dementia. As the data indicate an age pattern with greater proportions with more severe disease in the very old we restricted our analyses to studies reporting on severity <70, 70-79, and 80+ ages. Most of these studies reported severity based on the Clinical Dementia Rating scale (CDR): CDR=1 as mild, CDR=2 as moderate, and CDR=3 as severe dementia. Other studies report staging of dementia according to the Mini Mental State Examination (MMSE); DSM III criteria; the Functional capacity scale; the Cambridge Mental Disorders of the Elderly Examination (CAMDEX); the scale of Hughes and the Geriatric Mental State (GMS). We used a random effects meta-analysis to pool the data by severity level."

2.4.6.1. Methodology

Using the severity split and the associated disability weights we have computed an average disability weight for the three age group (<70, 70-80, 80+)

- Age<70: DW = 0.137
- 70 – 79, DW = 0.161

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– 80+, DW = 0.194

2.4.7. Rheumatoid arthritis

2.4.7.1. Disability weights by severity level

Table 2.7: Disability weight by severity levels for rheumatoid arthritis

Severity level	Health State	GHE 2015	GBD 2015	Severity Distribution
Mild	Musculoskeletal problems, upper limbs, moderate	0.117	0.117	48.8% (37.9-59.6%),
Moderate	Musculoskeletal problems, generalized, moderate	0.317	0.317	37.6% (29.3-46.2%)
Severe	Musculoskeletal problems, generalized, severe	0.581	0.581	12.2% (7.8-17.4%).

Source: IHME-GBD 2015 and WHO-GHE 2015

"To determine the proportion of people with RA within each of the severity levels, seven studies from three regions provided information on the severity of RA. Severity was classified according to Health Assessment Questionnaire scores, with the cut-off scores for each severity level: <1 mild; 1-1.875 moderate; and ≥2 severe. Estimates were pooled across studies. We used a random effects meta-analysis model. The pooled percentages were: mild 48.8% (37.9-59.6%), moderate 37.6% (29.3-46.2%) and severe 12.2% (7.8-17.4%). After streaming out 1,000 draws assuming a binomial distribution, percentages were scaled to sum to 1 at each draw. "

2.4.7.2. Methodology

Using the severity split and the associated disability weights we have computed an average disability weight for rheumatoid arthritis: DW = 0.24717

2.4.8. Osteoarthritis of the hip and Osteoarthritis of the knee

2.4.8.1. Disability weights by severity level

Table 2.8: Disability weight by severity levels for osteoarthritis

Severity level	Health State	GHE 2015	GBD 2015	Severity Distribution
Mild	Musculoskeletal problems, lower limbs, mild	0.023	0.023	47.0% (42.2-51.9%)
Moderate	Musculoskeletal problems, lower limbs, moderate	0.079	0.079	35.9% (31.3-40.7%)
Severe	Musculoskeletal problems, lower limbs, severe	0.165	0.165	17.1% (12.9-21.6%)

Source: IHME-GBD 2015 and WHO-GHE 2015

"To determine the proportion of people with OA within each of the severity levels, 4 studies from 3 regions provided information on the severity of OA. Severity was classified based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) with scores 0-5 taken as mild, 6-13 as moderate and 14 and higher as severe. Estimates were pooled across studies using a random effects meta-analysis model. The pooled percentages were: mild 47.0% (42.2-51.9%), moderate 35.9% (31.3-40.7%) and severe

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17.1% (12.9-21.6%) pooled between patient and physician ratings in a study from Bangladesh which we apply to low and middle income countries. The pooled proportions from three high income countries were: mild 74.3% (64.8-82.7%), moderate 24.3% (16.4-33.1%), and severe 1.1% (0.6-1.7%).”

2.4.8.2. Methodology

Using the severity split and the associated disability weights we have computed an average disability weight for osteoarthritis: DW = 0.038101

2.4.9. Low back pain

2.4.9.1. Disability weights by severity level

Table 2.9: Disability weight by severity levels for back pain

Severity level	Health State	GHE 2015	GBD 2015
Mild	Low back pain, mild	0.02	0.02
Moderate	Low back pain, moderate	0.054	0.054
Severe without leg pain	Back pain, severe, without leg pain	0.272	0.272
Severe with leg pain	Back pain, severe, with leg pain	0.325	0.325
Most severe without leg pain	Back pain, most severe, without leg pain	0.372	0.372
Most severe with leg pain	Back pain, most severe, with leg pain	0.384	0.384

Source: IHME-GBD 2015 and WHO-GHE 2015

Severity level Distribution

“The severity distributions are derived from an analysis of the Medical Expenditure Panel Surveys (MEPS) in the US.”

Table 2.10: Severity level distribution of back pain

Severity level	Distribution without leg pain	Distribution with leg pain
Mild	0.39 (0.29-0.50)	0.27 (0.18-0.37)
Moderate	0.36 (0.26-0.44)	0.37 (0.28-0.44)
Severe	0.11 (0.09-0.12)	0.13 (0.10-0.16)
Most Severe	0.15 (0.09-0.21)	0.23 (0.15-0.32)

Source: IHME-GBD 2015 and WHO-GHE 2015

“We used US claims data to derive the proportion of cases with low back pain who report leg pain.”

2.4.9.2. Methodology

We used 30% for the proportion of LBP with leg pain, which is quite conservative. Then, using the severity split and the associated disability weights we have computed an average disability weight for low back pain: DW= 0.125857

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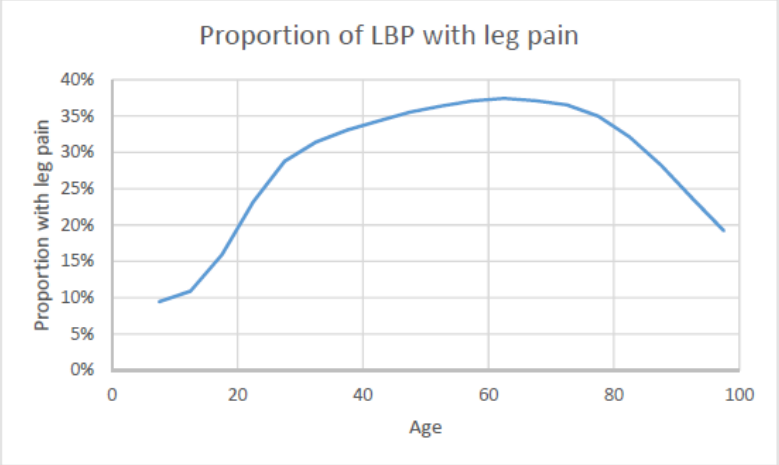

2.4.10. Cirrhosis

2.4.10.1. Disability weights by severity level

Table 2.11: Disability weight by severity levels for cirrhosis

Sequela	Health state	GHE 2015	GBD 2015
Cirrhosis	Decompensated cirrhosis of the liver	0.178	0.178

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.11. Lower Respiratory Infection

2.4.11.1. Disability weights by severity level

"The distribution of moderate (85%) and severe (15%) lower respiratory infections is determined by a meta-analysis of the ratio of severe to all LRI from studies that report the incidence of moderate and severe lower respiratory infections.

We used the health states of acute infectious disease episode, moderate and severe, with the lay descriptions and disability weight values shown in table below:"

Table 2.12: Disability weights for lower respiratory infection

Severity level	Health state	GHE 2015	GBD 2015	Severity Distribution
Moderate	Infectious disease: acute episode, moderate	0.051	0.051	85%
Severe	Infectious disease: acute episode, sever	0.133	0.133	15%

Source: IHME-GBD 2015 and WHO-GHE 2015

2.4.11.2. Methodology

Using the severity split and the associated disability weights we have computed an average disability weight for osteoarthritis: DW = 0.0633.

2.4.12. Cancers

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Disability weights for cancers are associated to the stage of the cancer.

2.4.12.1. Disability weights by severity level

Severity level	Health State	GHE 2015	GBD 2015
Primary stage	Cancer: diagnosis and primary therapy	0.288	0.288
Metastatic phase	Cancer: metastatic	0.451	0.451
Terminal phase	Terminal phase: with medication	0.540	0.540

Source: WHO-GHE 2015

As we don't model cancer's stages in the microsim tool, we are using the disability weight associated to diagnosis and primary therapy.

2.4.13. Injuries

We used the framework developed by IHME and explained in the supplementary appendix of (Vos et al., 2012[3]). They have created two matrixes. The first one (see Table 7.1 in Appendix) maps ICD10 codes to "23 nature of injuries". Each nature of injury refers to specific health states (long and short term disability weights). The second matrix (see Table 7.2 in Appendix) describes the proportion of the different natures of injuries in each cause of injury (Falls, Road accident, etc.).

We have used those two matrixes to compute an average short/long term disability weight for every injury modelled. When an individual is injured the short term disability weight applies until recovery or death. The individual is then attached to an injury sequela and the long term disability weight applies.

Table 2.13: Disability weight by severity levels for injuries

	Road injuries	Falls	Drowning	Self-harm	Interpersonal violence
Short Term	0.113	0.110	0.194	0.120	0.083
Long Term	0.141	0.119	0.157	0.018	0.110

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3. Risk factors

3.1. Modelling framework

We model every risk factor independently. They don't interact which each other.

3.1.1. Longitudinal trajectory modelling approach

All of the risk factors' longitudinal trajectories are modelled by assuming that each individual's relative position on the age and gender specific distribution of each risk factor remains constant over time. The value of the individual risk factor evolves over age and over time following the changes of the risk factor distribution over ages and years. Modelling a risk factor consists then in fitting continuous (or discrete) age-, year- and gender-specific distributions on cross-sectional data. This will be detailed in the next sections.

Box 3.1. Using uniform distributions to sample arbitrary distribution

The longitudinal trajectory modelling approach is based on the mathematical method which uses the uniform distribution for sampling from arbitrary distributions.

The probability integral transform states that if X is a continuous random variable with cumulative distribution function F_X then the random variable $Y = F_X(X)$, has a uniform distribution on [0, 1]. The inverse probability integral transform is just the inverse of this: specifically, if Y has a uniform distribution on $[0, 1]$ and if X has a cumulative distribution F_X, then the random variable $F_X^{-1}(Y)$ has the same distribution as X.

The main drawbacks of this method are first that we do not model a real longitudinal pattern. Indeed as we fit our distribution on cross sectional data, we do not model any longitudinal impacts. E.g. changing the prevalence of obesity in childhood does not have any impact on the distribution of obesity in adults 30 years later.

The second drawback of this approach is that we introduce a "selection bias". People at the top of the distribution are at higher risks. Then, they are more likely to die sooner than people at the bottom of the distribution. Consequently, the distribution of the quantile in a cohort -which is uniform at the beginning- tends to change. If the selection bias is too important, the model is not able to replicate correctly the risk factor distribution (see Box 3.1.). Nevertheless this selection bias is relatively limited.

3.1.2. How risk factors impact health

Risk factors impact disease incidence through relative risks. We assume that the relative risk we are using are "adjusted" meaning that they capture the effect of the specific risk factor adjusting for every other causes.

For every couple risk facto/disease we compute the **"baseline risk"** which combines the prevalence of the different risk categories and their associated relative risk (the computation is detailed in the next section for every relative risk.

For a single risk factor the conditional incidence, $I|Risk$ of a disease with an incidence I, knowing the risk profile is then:

$$I|Risk = RR * BaselineRisk * I$$

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For example, for smokers, with RR the relative risk for smokers versus non-smokers, we then have

$$I|Smoker = RR * BaselineRisk * I$$
$$I|Non\ Smoker = BaselineRisk * I$$

We assume that relative risks combine "multiplicatively", i.e. we multiply both relative risk and baseline risk to get the specific incidence of the global risk profile. We illustrate the formula below with smoking and BMI.

$$I|(Smoker\ \&\{BMI = 30\}) = RR(Smoker)BaselineRisk(Smoking) * RR(BMI = 30)\ BaselineRisk(BMI) * I$$

Risk factors impact only disease incidence, we do not model any effect on fatality, and this is a very conservative hypothesis.

3.2. Alcohol

3.2.1. Data

3.2.1.1. IHME Dataset

IHME dataset

We have access to the following dimensions for alcohol consumption in the IHME dataset:

- **Alcohol Consumption (g/day)**
- **Proportion of drinking events that are binge amongst binge drinkers**
- **Proportion of current drinkers**, defined as the proportion of individuals who have consumed at least one alcoholic beverage (or some approximation) in the last 12 months.
- **Proportion of binge drinkers**: defined as the *proportion of drinkers* who have had a binge event in the past 12 months. A binge event was defined as consuming 60 grams of alcohol approximately five drinks or more) in a single occasion for males and 48 grams of alcohol in a single occasion for females.
- **Proportion of former drinkers**
- **Proportion of lifetime abstainers**, defined as the proportion of individuals who have never consumed an alcoholic beverage.

WHO Dataset

We are using the Average daily intake in grams of alcohol among drinkers by country published by WHO in the GISAH (Global information system on Alcohol and Health) dataset. It's by gender and only for 2010.

3.2.2. Binge drinking

In the IHME dataset we have access to the prevalence of binge drinking among drinkers. We know from previous studies (Sassi, 2015[4]) that binge drinking is highly correlated with level of consumption. We then have built a model fitting the global prevalence of binge drinkers from IHME and introducing a correlation between alcohol consumption and drinking pattern.

This model on based on the OECD-CPD Alcohol model (Cecchini, Devaux et al. 2015). Pattern of drinking depends on the level of consumption. To determine the relationship between binge-drinking and quantity of alcohol consumed we are using data from the first wave of the cross-sectional component of the NPHS (National Population Health Survey 1994-95) (Statistics Canada 2012b) and several waves of

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the CCHS (Canadian Community Health Survey from 2000-01 to 2008-09) (Statistics Canada, 2012a). These cross-sectional surveys collect information related to health status, health care utilisation and health determinants for the Canadian population. They rely upon a large sample of respondents and are designed to provide reliable estimates at the health region level. The survey component on alcohol cover adults aged 15 and above.

From the survey's answers we are able to tabulate the probabilities of being a binger by category of quantity of alcohol consumed and by gender and age group.

Table 3.1 Pattern of drinking by category of quantity of alcohol consumed and by gender and age group, Canada

	Male					Female				
	15-19	20-29	30-44	45-64	65+	15-19	20-29	30-44	45-64	65+
0g/day - 5g/day	19%	22%	1%	11%	3%	13%	12%	4%	2%	1%
5g/day - 10g/day	44%	40%	2%	25%	7%	32%	30%	13%	8%	2%
10g/day - 20g/day	67%	66%	4%	47%	10%	66%	56%	32%	18%	4%
20g/day - 30g/day	81%	83%	6%	70%	20%	78%	77%	55%	36%	8%
30g/day - 40g/day	82%	91%	7%	83%	47%	83%	87%	71%	57%	35%
60g/day - 60g/day	93%	93%	8%	88%	46%	86%	89%	79%	63%	26%
+ 60g/day	96%	97%	9%	95%	95%	93%	97%	87%	93%	85%

We have then converted Table 3.1 into relative risks and used them to model the relationship between binge-drinking and quantity of alcohol consumed, assuming that this relationship is the same for all the EU countries. Using relative risk allow us to calibrate the probability of being a binger relatively to the alcohol consumption in fitting the average prevalence of binge drinking among the drinkers by age and gender (IHME).

3.2.3. Data corrections

We observe some inconsistencies in the IHM dataset. We have decided to rescale the data under the following assumptions:

3.2.3.1. Life Abstainer:

In the IHME dataset we do not observe that Life Abstainer + Current Drinker + Former Drinker = 100% as we should expect. To deal with this inconsistency we have use the following approach:

Before age 10: No Alcohol consumption. *LifeTime Abstainer* is set to 100%, and all the other categories to 0.

- After age 18: We use the lifetime abstainer proportion from IHME data, and we rescaled Former and current to match 100%
- Between age 10 and 18, we linear interpolate the value of life time abstainer on age, we rescale the proportion of former drinker and current drinker to match 100%.

3.2.3.2. Alcohol Consumption (g/day)

To take into account unrecorded alcohol consumption we have rescaled IHME average consumption (by age) to match the average alcohol consumption for adults published by WHO. We have based this

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rescaling on 2010 (where both IHME and WHO are available). We have assumed an absolute, gender specific, adjustment. In other words we keep the age distribution from IHME and we adjust the level based on WHO data.

3.2.4. Model

Alcohol is modelled through two dimensions: alcohol consumption (g/day) and pattern of drinking (binge-drinking).

For current drinkers, alcohol consumption is modelled with a truncated gamma distribution. According to (Rehm et al., 2003[5]) the gamma distribution is a good candidate for modelling alcohol consumption.

The gamma distribution is parametrized using the average alcohol consumption, $\bar{x}$, by age, gender and gender for every country. Based on results from (Kehoe, Gmel et al. 2012) we have calibrated the relationship between θ (the scale parameter of the Gamma distribution) and $\bar{x}$ with a power function.

$$AC(x) = \frac{\Gamma(\mathrm{x}, \mathrm{k}, \theta)}{\Gamma(200, \mathrm{k}, \theta)}$$

$$\theta = \exp(0.8907 \ln(\bar{x}) + 0.7001), k = \frac{\bar{x}}{\theta}$$

3.2.4.1. Drinking Initiation

A drinking initiation event is assigned to every individual. The event can only happened between 12 and 30 years old (after 30, the individual remains life-abstainer). The date of the event is calibrated to match the evolution of the life-abstainer curve.

Once the individual has passed the initiation event, his alcohol consumption is refreshed every year (at his anniversary).

3.2.4.2. Alcohol consumption and former drinker

Every individual maintain their positions in the evolving distribution of alcohol consumption.

The update of the alcohol consumption is made in two steps:

- Former drinker: made on a random basis based on the prevalence of former drinkers. If he is a former drinker his consumption is set to 0 for the 12 months.
- Daily consumption: determined on the basis of the individual's position on the gamma distribution.

3.2.4.3. Binge drinking

Every individual is assigned with a second quantile which determines his likelihood of being a binger. The two quantiles, the one for alcohol consumption q_1 and the one for binge drinking q_2 are independent –the correlation between consumption and binge drinking is included through the joint distribution computed as explained in 3.2.2.

$$\mathrm{AC} = \mathrm{F}^{-1}(\mathrm{q}_1), \qquad \mathrm{Binger} = \{\mathrm{q}_2 < \mathrm{p}_{\mathrm{binger}}\}, \qquad \mathrm{p}_{\mathrm{Binger}} = \mathrm{f}(\mathrm{AC})$$

3.2.5. Baseline risk and Relative Risk

We have used different relative risks from GDB-105 (2016)and from OECD-CDP Alcohol model (Cecchini, Devaux and Sassi, 2015[6]). As explained in (GBD Collaborators, 2016[7]), *"due to data availability, for high levels of consumption, uncertainty in the relative risk functions increases greatly. To minimize the uncertainty of these measures, relative risks were estimated up to the 90th percentile*

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of exposures in men (85 g/day) and the 95th percentile of exposures in women (60 g/day). For exposures beyond this, the associated relative risk was carried forward from these chosen percentile exposure levels. Though a dose-response relationship is evident at higher levels of exposure, the shape of the relative risk function is highly uncertain for higher levels of exposure both due to a lack of observations at these exposure levels, as well as confounding variables affecting estimation of the relative risk of these populations. Thusly, our relative risk estimates are likely an underestimate for the top 10% of male exposures and 5% of female exposures."

The theoretical minimum exposure measure is set to 1 for life abstainer. We also assume that former drinkers have a relative risk equals to 1.

Figure 3.1 Alcohol relative risks, for male aged 50.

Source: IHME – GBD 2015 and OECD CDP Alcohol (2015)

As seen in Figure 3.1**Erreur ! Source du renvoi introuvable.**, moderate consumption of alcohol may have a protective effect. We made the hypothesis that this protective effect doesn't exist anymore for bingers. The relative risk is then the maximum between 1 and the original relative risk. For injuries, we assume only bingers are at risk, relative risk is set to 1 for every non-binger.

3.2.5.1. For chronic conditions

We include binge drinking only when there is a protective effect. The formula is then the following

$$BR = \frac{1}{P_{la} + P_f + P_{CD}\int_0^{200}\left(P_B(x)AC(x)\max(1, RR(x)) + \big(1 - P_B(x)\big)AC(x)RR(x)\right)dx}$$

Where:

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- P_{la} Prevalence of lifetime abstainers
- P_f Prevalence of former drinkers
- P_{CD} Prevalence of current drinkers
- $P_B(x)$ Prevalence of binger for the level of consumption x
- $AC(x)$ Density function for alcohol consumption
- $RR(x)$ Relative risk function for current drinkers

3.2.5.2. For injuries

Only bingers are assumed to be at risk, the baseline risk is then:

$$BR = \frac{1}{P_{la} + P_f + P_{CD} \int_0^{200} \Big(P_B(x) AC(x) RR(x) + \big(1 - P_B(x)\big) AC(x) \Big)\, dx}$$

Where:

- $RR(x)$ Relative risk function for current drinkers

3.3. Blood Pressure

3.3.1. Data

NCD RISC Dataset (published in the Lancet in 2016).

- Timeframe: 1975 – 2014
- Country coverage: most of the country in the world
- Description: average systolic and diastolic blood pressure and proportion of people with SBP > 140 by age group (18-19, 20-24, …, 80-84, 85+)-and gender.

3.3.2. Model

Blood pressure is modelled with a log-normal distribution.

$$SBP(n, y) \rightsquigarrow LogNormal(\hat{\sigma}(n, y), \hat{\mu}(n, y))$$

To fit the parameters of the log-normal distribution, we are only using the average systolic blood pressure, $\overline{SBP}$, and proportion of people with high blood pressure, $P_{BP>140}$. The naïve fitting of the log normal distribution, for each data pair ($\overline{SBP}$, $P_{BP>140}$), a unique pair mean and standard deviation, is not satisfying (leading to some implausible distributions). We then decided to constraint the evolution of the standard deviation by age. For each year, we have optimized the following system:

$$\min_{\lambda(y)} \sum_n \left(\overline{SBP} - e^{\hat{\mu}(n,y) - \frac{1}{2}\widehat{\sigma^2}(n,y)} \right)^2$$

$$\hat{\sigma}(n, y) = \sigma_0 + \lambda(y) \cdot (n - n_0)$$

$$\hat{\mu}(n, y) = \ln(140) - \Phi^{-1}(1 - P_{BP>140})$$

n_0 is the first available age (here 18) and σ_0 is computed to match the data ($\overline{SBP}$, $P_{BP>140}$) for the first available age group (here 18-19).

Figure 3.2: Fitting gamma distribution on average blood pressure and share of people with raised blood pressure, (Dataset: France – female – 2015)

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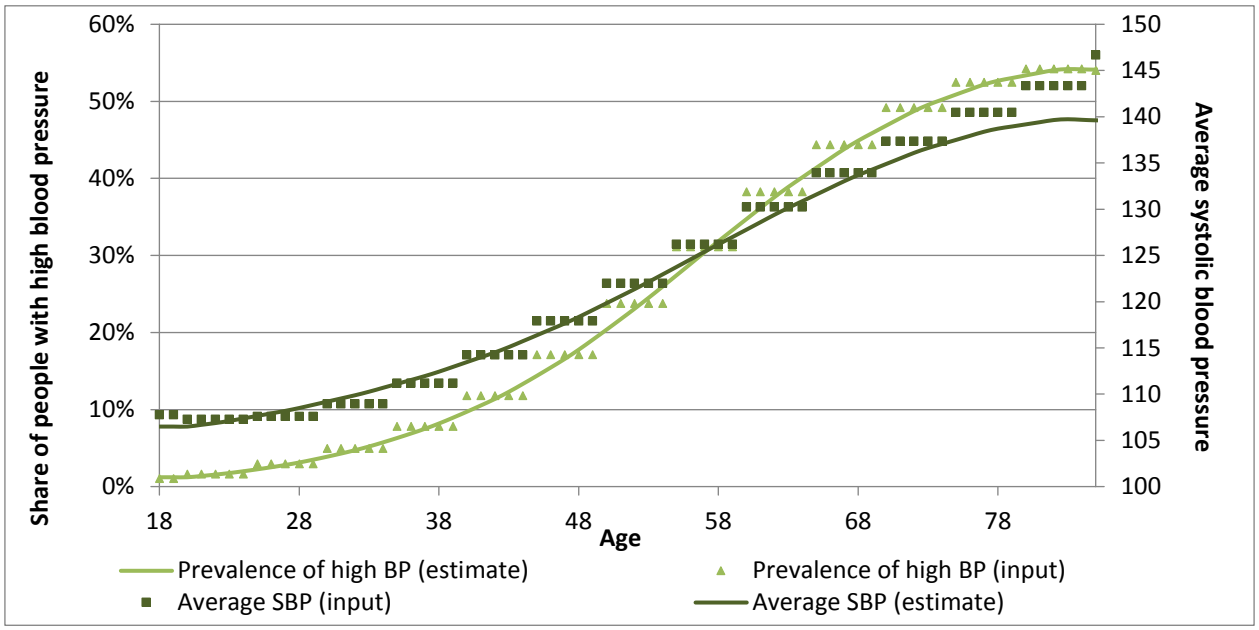
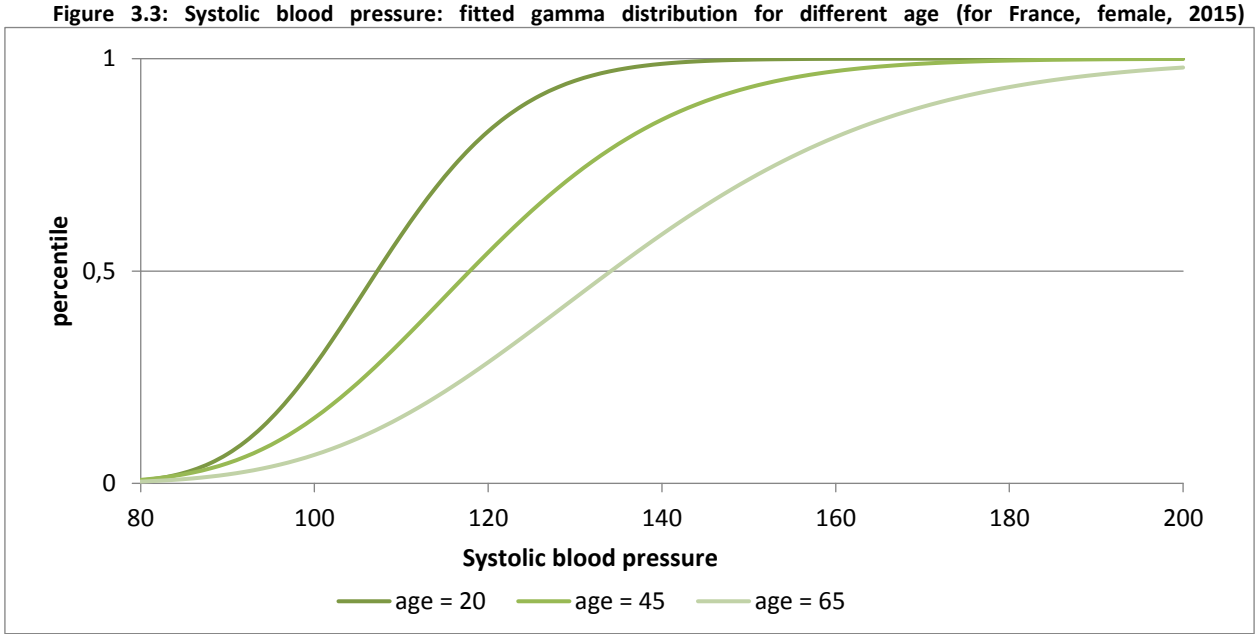


This methodology puts more weight in fitting the percentage of high blood pressure than the average systolic blood pressure, and assumes the deviation of blood pressure depends linearly on age.

Figure 3.3: Systolic blood pressure: fitted gamma distribution for different age (for France, female, 2015)



Blood pressure rises with age. An individual at the 50th percentile has its blood pressure raised from 107 at 20, to 117 at 45 and to 134 at 65.

3.3.3. Relative risks and baseline risk

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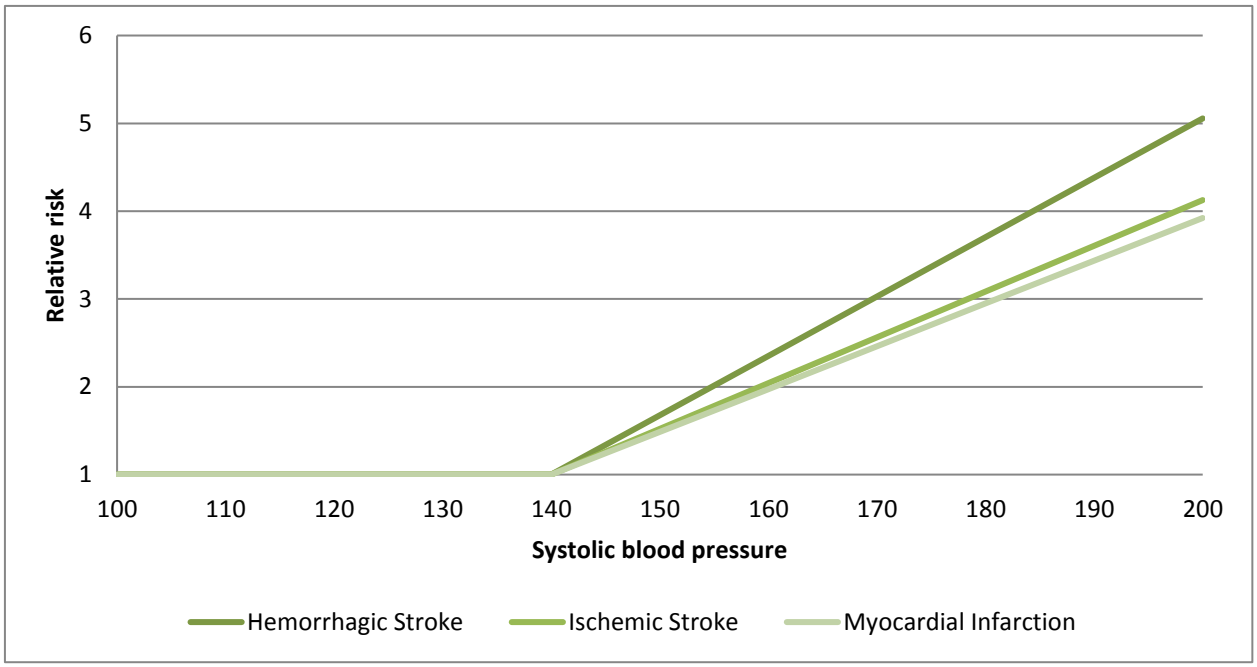
Relative risks for BMI are provided by IHME through a linear function (scale depends on age).

Figure 3.4: Relative risk for blood pressure, male and female aged 50, source IHME – GBD2015



Source: IHME – GBD 2015

For each disease, the baseline risk is computed as following:

$$BR = \frac{1}{\int_{80}^{250} RR(x)dBP(x)}$$

3.4. BMI

3.4.1. Data

NCD RISC Dataset (published in the Lancet in 2016).

- Timeframe: 1975 – 2014
- Country coverage: most of the world's countries.
- Description: prevalence of 7 categories of BMI by gender and age-groups.

3.4.2. Model

BMI is modelled as a continuous variable with a cumulative distribution function piecewise linear (calibrated in order to match the prevalence of the 7 BMI categories available). We use 10 and 150 for BMI boundaries.

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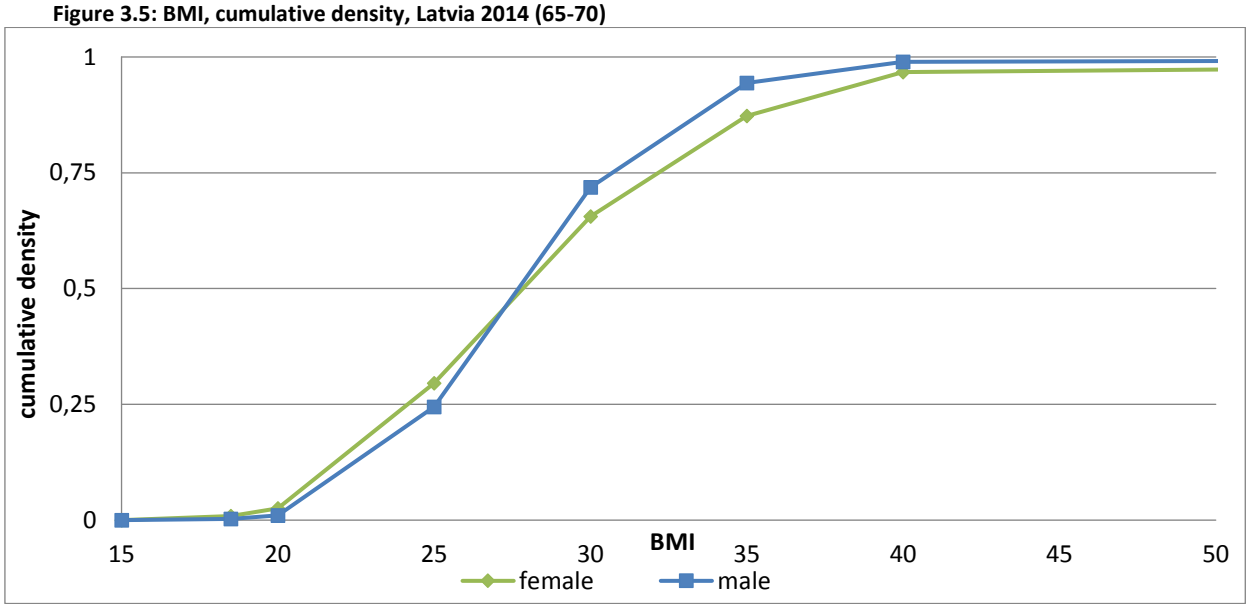
It was not possible to find a simple functional form which matched the level of both obesity and morbid obesity. As the categories of BMI are quite small, a uniform distribution inside the categories is a coherent assumption.

Figure 3.5: BMI, cumulative density, Latvia 2014 (65-70)

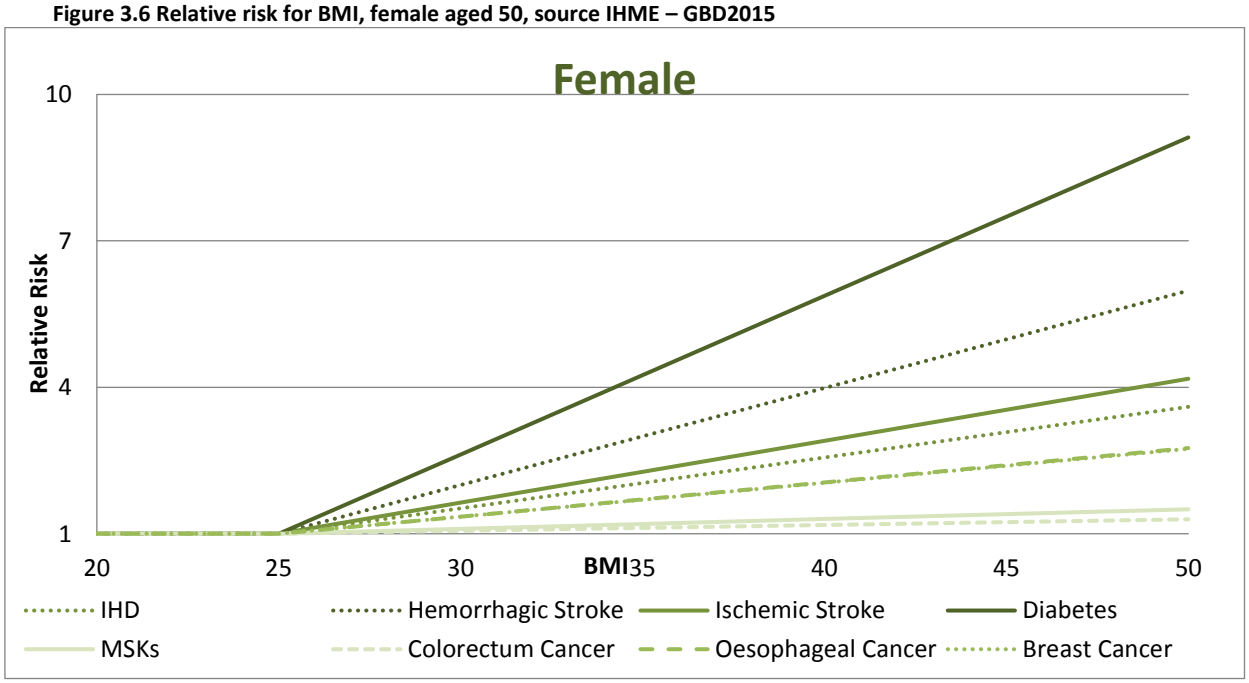


Source: NCD RISC (2016)

3.4.3. Relative risks and baseline risk

The relative risk is provided by (2016) through a linear function.

Figure 3.6 Relative risk for BMI, female aged 50, source IHME – GBD2015



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Source: IHME – GBD 2015

For each disease, the baseline risk is computed as following:

$$BR = \frac{1}{\int_{10}^{150} RR(x)dBMI(x)}$$

3.5. Physical Activity

3.5.1. Data

We are using the data from GDB 2015 (Institute for Health Metrics and Evaluation (IHME),(n.d.)[8]). They measure the average weekly physical activity at work, at home, transport related and recreational measured by MET min per week. We have access to the prevalence –by gender, age-group, and every 5 year (1990-2015) - of the 4 categories described below[1]:

- Inactive (bellow 600 METs)
- Low active (between 600METs/week and 4000 METs/week)
- Moderately active (between 4000 METs and 8000 METs/week)
- Highly active (more than 8000METs/week).

3.5.2. Model

Physical activity is modelled through the average weekly physical activity at work, at home, transport related and recreational measured in METs/week as a continuous variable with a cumulative distribution function piecewise linear (calibrated in order to match the prevalence of the 4 categories available). We use 400 and 10000 METs/week for physical activity boundaries.

[1] 600 METs a week corresponds to WHO guidelines for physical activity: 150 minutes of moderate activity or 75 minutes of intense activity.

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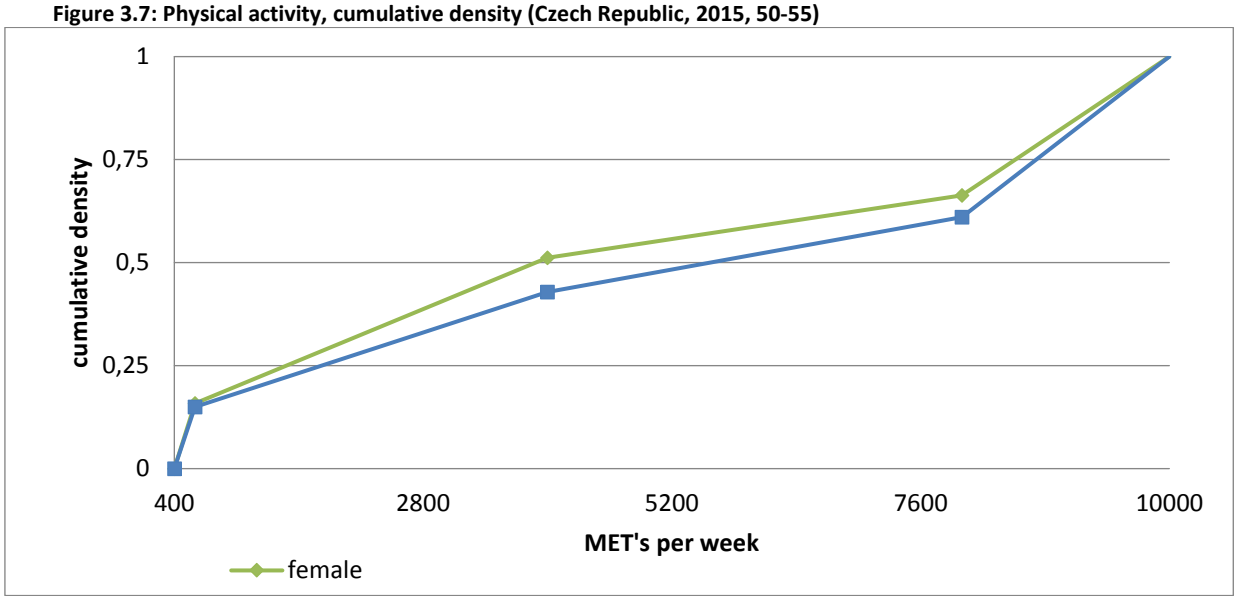
Figure 3.7: Physical activity, cumulative density (Czech Republic, 2015, 50-55)



Source: IHME – GBD 2015

3.5.3. Relative risks and baseline risk

The relative risk are provided by (2016) by categories of physical activity level.

Table 3.2: Relative risk for categories of physical activity (Male and Female aged 50-55)

	Inactive	Low active	Moderately active	Highly active
Colorectal Cancer	1.293	1.172	1.067	1
Breast Cancer	1.159	1.12	1.09	1
Myocardial Infarction	1.301	1.103	1.019	1
Ischemic Stroke	1.349	1.142	1.098	1
Diabetes	1.387	1.189	1.037	1

Source: IHME – GBD 2015

For each disease, the baseline risk is computed as following:

$$BR = \frac{1}{\sum RR_{PA\ level} \cdot P(PA\ level)}$$

3.6. Smoking

3.6.1. Data

We are using the data from GDB IHME2015 –Tobacco Visualization (Institute for Health Metrics and Evaluation (IHME),(n.d.)[9]). They provide the prevalence of daily smokers by gender and age-group from 1980 to 2015 (every 5 years).

3.6.2. Model

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Smoking is modelled as a dichotomous variable, smoker/non-smoker. A quantile is assigned to every individual at the beginning of its life and remains the same during its entire life. Every time year or age changed we compare the value of this quantile to the prevalence of smokers. If it is below the individual is defined as "current smoker".

3.6.3. Relative risks and baseline risk

We used relative risk published in the GDB 2015 study (GBD Collaborators, 2016[7]) (for CVD's), and from DYNAMO-HIA (for COPDs and Cancers). In GDB 2015, relative risks are defined for smokers/non-smokers, whereas in DYNAMO-HIA they are described for Never Smoker/ Former Smoker/Smoker. As we don't really model the longitudinal trajectories of smoking, plus as we don't have access to never smoker in IHME database, we have preferred to convert those last relative risks into (smokers/non-smokers) using prevalence also published by DYNAMO-HIA. This assumption leads to underestimate the impact of tobacco's reduction policies.

Table 3.3: Relative risks for smoking

Disease	Source	RR Smoker vs non-smoker Female	RR Smoker vs non-smoker Male
Diabetes	GBD	1.426	1.102
Stroke	GBD	2.882	3.777
IHD	GBD	2.952	3.843
COPD	DYNAMO-HIA	3.768	4.46
Oesophagus Cancer	DYNAMO-HIA	2.296	5.061
Lung Cancer	DYNAMO-HIA	3.871	6.643

For each disease, the baseline risk is computed as following:

$$BR = \frac{1}{P(NonSmoker) + RR\,P(Smoker)}$$

4. Data and Methods: Cost of illnesses calculations, to include in the microsimulation model

4.1. General estimation approach

Our goal is to predict the total medical costs, for each patient, conditional on age, gender, and the FRESHER disease status. In a first step, we decided to use 3 "sources" countries (Estonia, France, Netherlands), for the 3 areas of FRESHER. What follows concerns the methodology applied in the French dataset, but a similar methodology has been used for the two other sources countries.

The general cost formula is as follows:

$$Cost_{i,total} = Cost_{i,residual} + Cost_{i,extra-main} + Cost_{i,extra-comorb} + Cost_{i,extra-death} \quad (1)$$

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For a person *i* with no FRESHER- modelled diseases, the total medical costs will be equal to what we call the age and gender-specific residual costs. It is important to emphasize that this component does not apply to completely healthy people, but rather is an average of medical costs for those who do not have any FRESHER-modelled diseases. If people have only one FRESHER-defined disease, their total cost will be equal to the sum of their predicted residual cost and the predicted extra cost of having this disease. If people have two diseases, the comorbidity cost component will also be added to this sum, as explained below. Due to the data limitations, the comorbidity component does not take into account more than two explicit diseases.

Box 4.1. Defining main diseases and comorbidities

For our modelling purposes, we assume that the "main disease" (the extra costs for which are estimated as described in section 4.2.1 below) is the most recently diagnosed one, and the "comorbidity" (the extra costs for which are estimated in step 4.2.2) is a disease which was diagnosed earlier. For example, if a person has had diabetes for several years, and was diagnosed with cancer this year, then we would first estimate the extra cost of having a "main disease"- cancer (in the sample with comorbidities) as in section 4.2.1, and then estimate the extra cost of having a comorbidity-diabetes- in the presence of cancer, as in equation (8).

In principle, one could predict the total medical costs –also including out-of-pocket spending– for each person *i* by estimating the parameters in the two-way interaction model (for both genders separately) as described in (Cortaredona and Ventelou, 2017[10]) :

$$\ln(Cost_i) = \alpha + \beta \cdot age_i + \gamma_k \cdot D_{i,k} + \gamma_j \cdot D_{i,j} + \gamma_{kj} \cdot D_{i,k} \cdot D_{i,j} + \varepsilon_i \quad (2)$$

Where $Cost_i$ is a total medical cost, defined as follows:

"In a bottom-up design, units of health care are used on a patient level and are multiplied with a price for this unit. All individual health expenditures are then summed up to calculate total cost of the disease (Cortaredona and Ventelou, 2017[10])*"*

In addition, age_i corresponds to age; $D_{i,k} = 1$ if individual i suffers from illness k, =0 otherwise. It follows that $D_{i,k} \cdot D_{i,j} = 1$ if $D_{i,k} = D_{i,j} = 1$, i.e.: if individual i suffers simultaneously from illness k and illness j, and ε_i is an error term. The intercept α represents the predicted medical cost for a person aged 18-39, without any diagnosed FRESHER disease (=residual cost).

Model (2) can be estimated using the sample of people with positive costs using multivariate gamma regression with a log link (see (Thiébaut, Barnay and Ventelou, 2013[11]))for the choice on appropriate econometric specification for France).

For example, the total predicted medical cost for a person aged 55 with no FRESHER diseases and with positive costs would be equal to:

$E(C|C>0) = \exp(\hat{\alpha} + \hat{\beta}_{50-55})$

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For a person with diabetes of the same age, the total predicted cost in this sample would be equal to:

E(C|C>0, diabetes=1)= $\exp(\hat{\alpha} + \hat{\beta}_{50-55} + \hat{\gamma}_{diabetes})$

For a person with both diabetes and cancer, the total cost in the sample of people with positive costs can be predicted as:

E(C|C>0, diabetes=1; cancer=1)= $\exp(\hat{\alpha} + \hat{\beta}_{50-55} + \hat{\gamma}_{diabetes} + \hat{\gamma}_{cancer} + \hat{\gamma}_{cancer*diabetes})$

To make sure that these predicted costs are representative not just of the people with positive medical costs, but of all the people with the diagnosed conditions[2], an adjustment should be made by multiplying these costs by the probability of having positive medical costs. For example, the total predicted cost for a person with diabetes is:

E(C|diabetes=1)= P(C>0)*E(C|C>0, diabetes=1)

The first part of this two-part model estimator can be estimated using logit regression:

$$P(C > 0) = \Phi(\mathrm{a} + \mathrm{b} \cdot \mathrm{AGEcat})$$

where Φ is the cumulative standard logistic distribution function.

We will explain later the rationale for why we estimate the probability P(C>0), rather than P(C>0|diabetes=1).

The practical problem with estimating model (2) is that the sample size for several conditions in the Échantillon généraliste des bénéficiaires (EGB), the dataset available in France, is too small for two-part model estimation with interactions. Predicting costs using model (2) is even more problematic if we want to take into account the information on the length of time since diagnosis contained in the EGB dataset. Therefore, it was decided that the total medical costs in France (and, for consistency, in all other countries) will be predicted by separately estimating each component listed in equation (1), as described in the sections that follow.

4.2. Cost component estimation

4.2.1. Extra cost of disease: $Cost_{extra,main}$

As discussed in (Cortaredona and Ventelou, 2017[10]) , extra disease costs are estimated as "the mean marginal difference of the predicted outcome with a disease variable switched on or off". There are two different (but related) approaches, depending on whether there was chronic disease comorbidity.

[2] This adjustment is necessary because not all diagnosed people will incur positive medical expenditures.

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In general, average medical cost for any age and gender can be predicted as follows:

$$E(C) = P(C > 0)*E(C|C > 0)+ P(C=0)*E(C|C = 0) = P(C > 0)*E(C|C > 0) \quad (3)$$

The extra cost of a disease can therefore be estimated, for a given gender and age group, as the difference in the predicted costs, conditional on the disease status:

$$\widehat{Cost}_{extra} = P(C>0|disease=1)*E(C|C>0,disease=1) - P(C>0|disease=0)*E(C|C>0,disease=0) \quad (4)$$

Another way to think about the first part of this formula is that E(C|C>0,disease=1) component is representative of the population with a given disease who have positive medical expenditures, while multiplication by P(C>0|disease=1) factor makes such costs representative of the medically diagnosed population with a disease (who may or may not have positive medical expenditures).

Estimating the first part (i.e. the probability) components of the two-part model (4) is however complicated, because for a number of diseases in France (and for all diseases in Estonia), the disease definition in the administrative data depended on whether positive costs were reported. Therefore, estimating P(C>0|disease=1) was generally impossible. Even when this was not strictly the case (i.e. when a small proportion of patients with a disease had zero costs as in France), it was decided that estimating P(C > 0|disease=1) was not a feasible option because the disease definition was strongly endogenous to the probability of having nonzero expenditures[3].

Using (3) and (4), we are able to estimate the extra costs of diseases using the following formula:

$$\hat{C}_{|disease=1} - \hat{C}_{|disease=0} = P(C>0)E(C|C>0,disease=1) - P(C>0)E(C|C>0,disease=0) \quad (5)$$

Equation (5) was estimated in two samples:

a) Without any comorbidity (i.e., predicted average costs were compared among patients with a disease and without a disease, in the sample with no other chronic diseases, whether FRESHER-defined, or any other chronic conditions), and

[3] As one can see, the first part probability is predicted unconditional of the disease status (but conditional of age). This is not ideal, because the probability of having non-zero costs is likely to be higher in the sample of sick people than in the sample of healthy people. To deal with this, one could have assumed, for example, that the probability of having non-zero expenditures was equal to 1 in the sample of people with a disease. However, this assumption is arbitrary and it might lead to cost overestimation. On the other hand, our decision to use P(C>0) probability in the first part is likely to lead to a more conservative extra cost estimation.

In any case, our estimates suggest that the difference between these probabilities is relatively small in the middle ages and for the elderly (i.e., in the 50-90 y.o group), especially among women (e.g., P(C>0|d=0, females, age=60-64)=0.94; P(C>0|d=1, females, age=60-64)=0.99; P(C>0|d=0, males, age=60-64)=0.98; P(C>0|d=1, males, age=60-64)=0.90. In the samples with at least one comorbidity, there is very little difference in the predicted probabilities depending on the main disease status.

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b) In the sample with at least one comorbidity (whether FRESHER-defined, or any other chronic conditions), the predicted costs for patients without a disease of interest were subtracted from predicted costs for patients with a disease of interest.

The parameters in the second part of the two part model as described by equation (5) were estimated similar to model (2), but without the interactions, and with a dummy for a given disease of interest (rather than for a vector of diseases):

$$\ln(Cost_i) = \alpha + \beta \cdot age_i + \gamma_k \cdot D_{i,k} + \varepsilon_i \quad (6)$$

For example, the extra cost of diabetes for a woman aged 55 is predicted using parameters estimated in model (5) as follows (separately for samples with and without any comorbidities):

$$= \Phi(\hat{a} + \hat{b}_{50-55}) \times \left[\exp\left(\hat{\alpha} + \hat{\beta}_{50-55} + \gamma_{diabetes}\right) - \exp(\hat{\alpha} + \hat{\beta}_{50-55})\right]$$

$\Leftrightarrow$

$$\widehat{Cost}_{extra} = \frac{\exp(\hat{a}+\hat{b}_{50-55})}{1+(\hat{a}+\hat{b}_{50-55})} \times \left[\exp\left(\hat{\alpha} + \hat{\beta}_{50-55} + \gamma_{diabetes}\right) - \exp(\hat{\alpha} + \hat{\beta}_{50-55})\right] \quad (7)$$

4.2.2. Extra cost of comorbidity: $Cost_{extra,comorb}$

The extra (extra) cost of comorbidity is estimated as the difference in the predicted costs for patients with both the "main" disease and comorbidity (as defined above) versus the predicted cost for patients with just a "main" disease:

$$\widehat{Cost}_{comorb} = P(C>0)E(C \mid C>0, comorb=1, disease=1) - P(C>0)E(C \mid C>0, comorb=0, disease=1) \quad (8)$$

The parameters for this equation are estimated using a model similar to (2) shown above, i.e. including not only the main disease parameters, but also their interactions. However, as already mentioned, we could not estimate this model for every single disease, nor could we take into account the length of time since diagnosis because of the sample size limitations. Therefore at this step, we had to combine several diseases into groups (e.g. this applied to both types of strokes and all cancers). In addition, to reduce potential for residual confounding, a dummy was also included to control for long-term non-FRESHER chronic diseases in the case of Estonia and France analyses. An intercept in this model thus represents an average costs for people without any chronic diseases for people aged 18-39.

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4.2.3. Extra cost of death: $Cost_{extra,death}$

In the French case, extra cost of death was estimated using a similar two-part modelling approach, as the mean marginal difference of the predicted outcome (total health expenditure in 2014) with a death dummy (corresponding to dying in the first semester of 2015) switched on or off. As the data on costs accumulated throughout 2014 was available, and the information on whether a person died was provided for 2015 as well, this difference was estimated for people who died in the first semester of 2015, compared to the people who stayed alive in the same period. Including people who died in the second semester of 2015 in the analysis was ruled out because the date of death for them was too far away from 2014, and therefore it was likely that the extra cost of death would be underestimated for them.

We conducted this analysis separately for two samples: with at least one FRESHER-defined NCD, and without any NCDs. These costs were then added on top of the other medical expenditures. To avoid the issue of potential double-counting of the death-related costs, the main cost analysis was restricted to the people who were still alive on 31 December 2014, and therefore proportion of those who died in the first semester of 2015 was small in relation to the total. In Estonia, the Netherlands and the UK, it was impossible to estimate extra deaths costs using this approach due to data limitations, and therefore for these countries they were extrapolated from the French ones using the approach described below.

4.3. Residual cost and related issues

We estimate age- and gender-specific average residual costs by restricting the sample to people who had no FRESHER- defined diagnosed diseases (but could have other diagnosed conditions, including chronic ones). Such people may or may not have had zero health expenditures.

A potential complication is that in FRESHER simulations, people are assigned disease status based mostly on IHME epidemiological prevalence (with some additional calibrations as appropriate), which may well be different from the administrative dataset-based prevalence. In France, the administrative dataset is nationally representative and includes all people covered by national health insurance (both consumers and non-consumers). It may thus inappropriately classify people with undiagnosed FRESHER conditions as being “healthy”, whose costs will therefore be part of the residual costs by definition. In Estonia, the sample is restricted to users of healthcare, plus the artificial sample based on the Estonia Census to add age groups which are representative of the national age-gender distribution. Therefore, Estonia analytical sample may also include people who have undiagnosed FRESHER conditions, and whose costs will form part of the residual costs. Such costs will also not be captured when estimating the extra cost of disease as described in section 4.2.1.

One potential way to deal with this is to assume that IHME-based prevalence reflects “correct” epidemiological prevalence (i.e. including both diagnosed and undiagnosed cases). Under this assumption, we could in theory adjust the predicted costs of disease by multiplying it by some factor based on the difference between “diagnosed” and “real” prevalence. If we find, for example, that for women aged 50-59, the prevalence of diabetes based on administrative data is 10%, while IHME-based prevalence is 12%, then we could multiply the estimated extra cost of disease in this group by 10/12=0.83, to make sure that such costs are representative of women who are both diagnosed and undiagnosed. Alternatively, we could assume that the extra disease cost equals zero for the proportion of people who

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is undiagnosed according to IHME data. Likewise, we could re-categorize our residual costs accordingly, which is likely to increase residual costs because a number of cases with zero expenditures will be reduced. Therefore the net effect on the total costs is ambiguous.

Nevertheless, it is not certain that IHME-estimated disease prevalence is necessarily superior to the administratively-derived one, as it relies on data of varying quality and methodological basis (e.g. it can be based on multiple sources of survey data, with additional assumptions to correct for self-reporting bias). Some analysis (see below) shows that for example in France, age and gender-specific prevalence of diabetes and of several cancers is higher in the administrative than in the IHME dataset, which suggests this divergence may not be due to the inclusion of undiagnosed cases in IHME data. Although in some other cases, the prevalence was considerably higher in the IHME dataset, this was mostly true at the oldest and the youngest ages, where IHME estimation methodology might rely on too little data and on too many assumptions. In addition, at the oldest ages (generally older than 60-70), where the prevalence rates diverge the most, the absolute numbers of affected people gets lower with each year of life, therefore the total impact on costs is more limited than the actual graph may suggest. Therefore, we prefer not to further adjust the extra disease/residual costs. Besides, since we are interested mostly in the "delta effect" of different interventions/scenario comparisons, the potential overestimation issue stemming from assigning the estimated costs to the undiagnosed cases is probably of minor significance.

Figure 4.1. Diabetes prevalence by gender, France

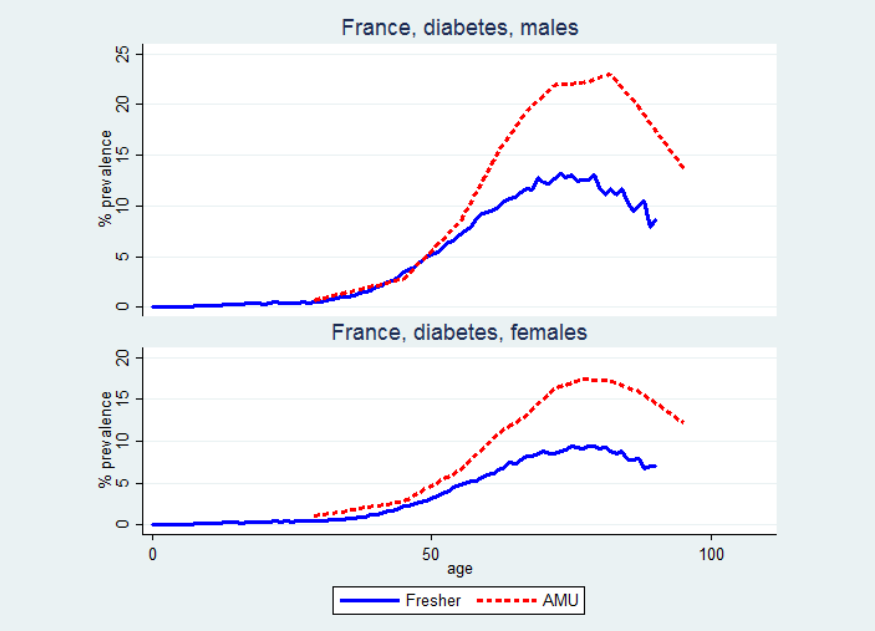

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Figure 4.2. Lung cancer prevalence by gender, France

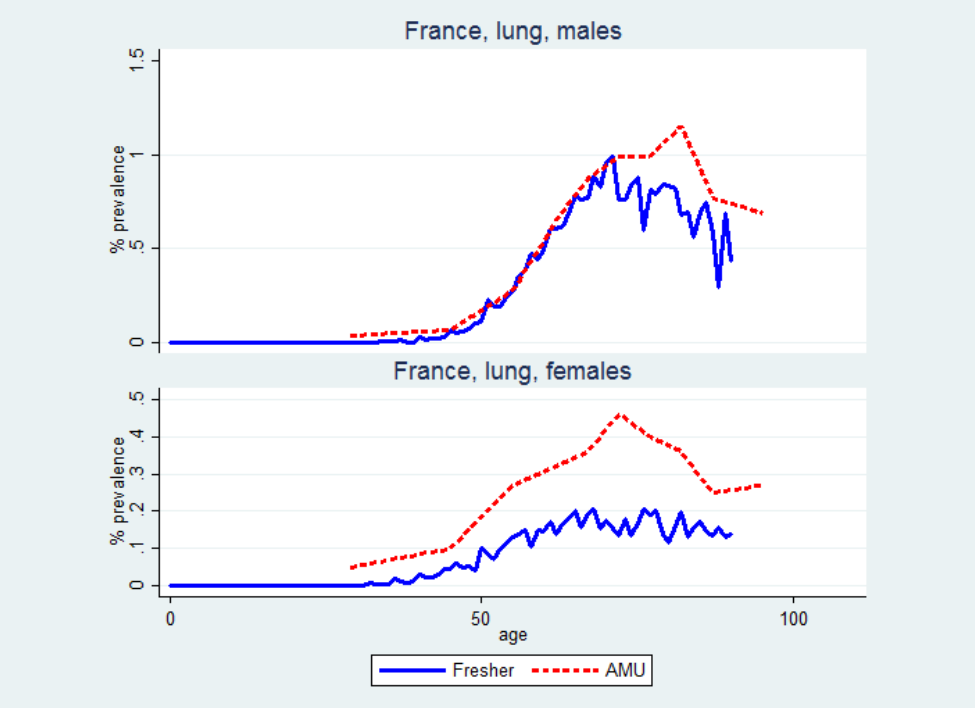

Figure 4.3. Colorectal cancer prevalence by gender, France

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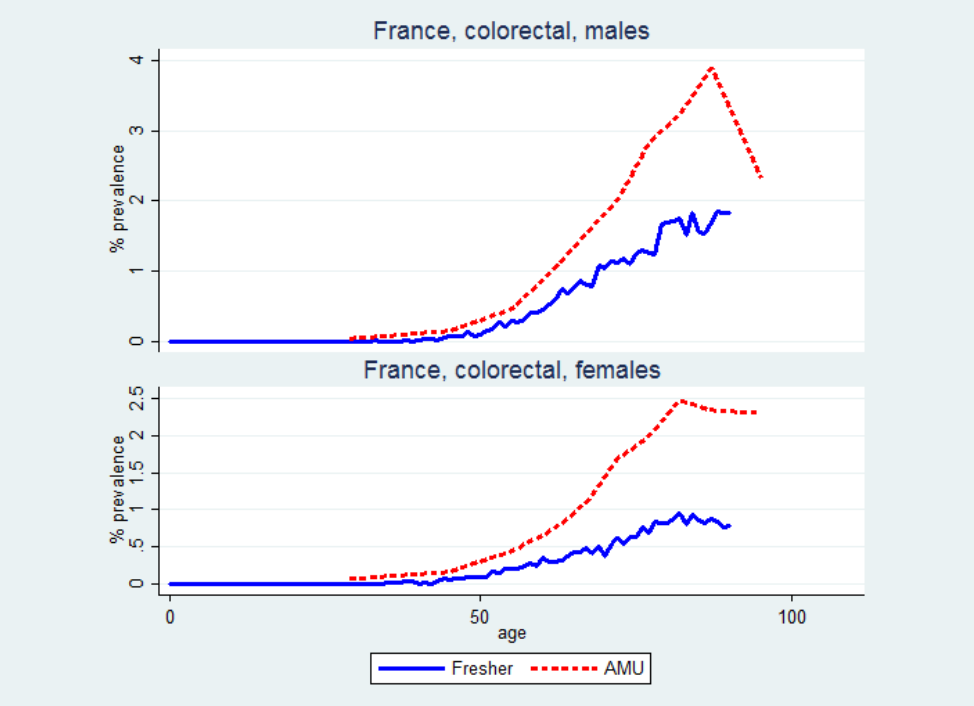

Figure 4.4. Breast cancer prevalence, France

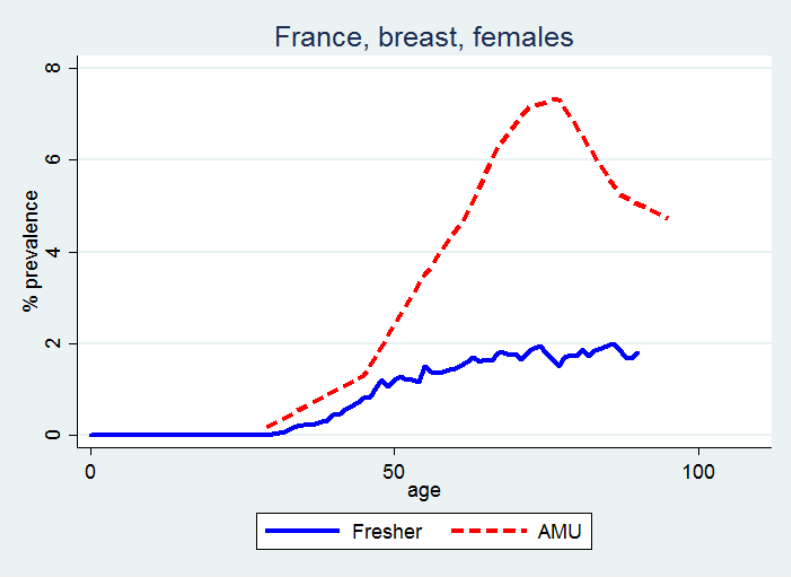

Figure 4.5. COPD prevalence by gender, France

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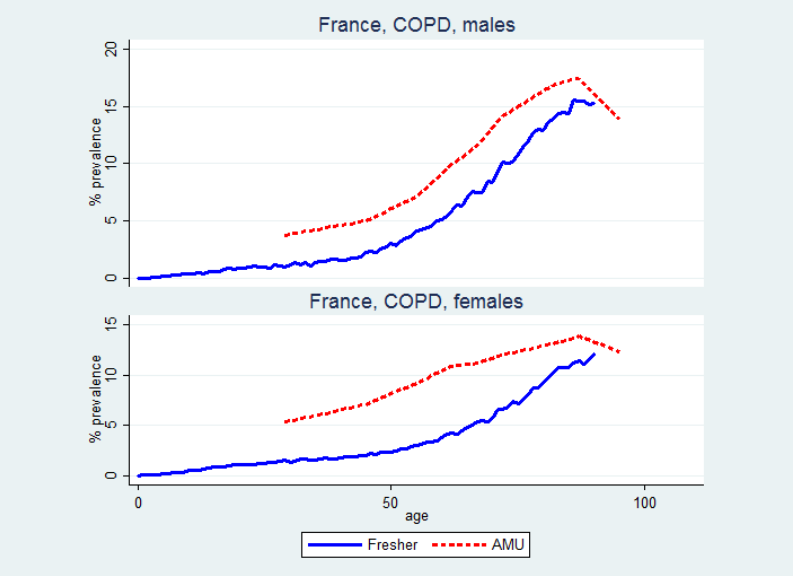

4.4. Cost extrapolation to other countries

The annual disease costs were estimated for the three anchor countries (France, Estonia and the Netherlands), and then extrapolated to three EU regions: Southern Europe; Central/Eastern Europe and Northern Europe. As per the Grant Agreement, the EU member countries were grouped into regions as follows (anchor country highlighted in bold):

- Southern Europe (Croatia, Cyprus, **France**, Greece, Italy, Malta, Portugal, Slovenia and Spain);
- Central/Eastern Europe (Bulgaria, Poland, Romania, Slovakia, **Estonia**, Hungary, Latvia and Lithuania);
- Northern Europe (Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Ireland, Luxembourg, the **Netherlands**, Sweden and United Kingdom).

Our extrapolation methodology is based on the assumption that the annual treatment cost differentials between countries are time-invariant, and that they are mostly driven by the differences in two components: cost per unit of treatment received, as well as the population-level intensity of treatment provided. For example, the spending per capita for inpatient costs can be broken down as follows:

$$\frac{Spending}{Capita} = \frac{Spending}{Discharge} \times \frac{Discharges}{Capita} \quad (9)$$

Where $\frac{Spending}{Discharge}$ can be viewed as the average price per unit of inpatient treatment received, while $\frac{Discharges}{Capita}$ represents the population-level "intensity" of hospitalization received in a given country. Then, one can divide spending per capita for inpatient treatment in country a by spending per capita in

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country b, and multiply the costs in an anchor country by this ratio to extrapolate to a comparator country.

Given that the cost of treatment is also determined by other components, we also estimated $\frac{Spending}{Capita}$ ratios between countries for outpatient and pharmaceutical costs. For outpatient costs, for example, this ratio can be viewed with similar interpretation:

$$\frac{Spending}{Capita} = \frac{Spending}{Visit} \times \frac{Visits}{Capita} \quad (10)$$

To estimate these differentials, we used the OECD data[4] on the inpatient curative and rehabilitative care spending/capita; outpatient curative and rehabilitative care spending/capita; medical goods spending/capita. To ensure comparison, we used this data for the same year- 2014, expressed in constant prices, OECD base year.

To see that it's not enough to rely on ratios of the spending per unit of care provided, and that it's also necessary to take into account the treatment intensity component, consider the case of extrapolating outpatient costs from France to Portugal.

Table 4.1. Outpatient cost ratio estimation: extrapolating from France to Portugal

Country	spending/ visit	visits/ capita	spending/ capita	Ratio, incorrect	Ratio, correct
France	97	6.7	650		
Portugal	141	4.1	579	1.45	0.89

*Estimated as a ratio of $\frac{Spending}{Visit}$ in Portugal to France

**Estimated according to formula (10)

The incorrect ratio of 1.45, estimated as the spending/visit ratio of costs, suggests that the outpatient costs are considerably higher in Portugal, while the correct ratio suggests that the opposite is true. The explanation is that the incorrect ratio does not take into account the population-level intensity of outpatient visits, which seem to be considerably higher in France.

After estimating the differentials in these three components, we take them all into account when estimating the overall disease-specific conversion factor between countries. It's possible, for example, that diseases in the more acute stage, such as myocardial infarctions and strokes, have a much greater inpatient component than for example diabetes. Therefore, the overall disease-specific conversion factor to extrapolate between countries can be represented by the formula:

$$\text{Conversion factor} = \sum_{i=1}^{3} (x_i \times w_i) \quad (11)$$

[4] http://stats.oecd.org

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Where x_i is the ratio of per capita inpatient; outpatient or pharmaceutical spending between countries (based on OECD data); w_i are the weights assumed to represent treatment proportions for each disease. These weights were also obtained based on the OECD SHA data on the expenditure by disease, in millions national currency units. For example, for the Netherlands (used for extrapolating in the Northern and Southern regions), the following table was estimated:

Table 4.2. Treatment component weights by disease, Netherlands (for Southern and Northern regions extrapolation)

	Inpatient	outpatient	pharma	Inpatient, %	Outpatient, %	pharma, %
Ischemic stroke	3089	915	962	62.20%	18.40%	19.40%
Haemorrhagic stroke	3089	915	962	62.20%	18.40%	19.40%
MI	3089	915	962	62.20%	18.40%	19.40%
Cancers	2492	559	460	71.00%	15.90%	13.10%
Diabetes	267	503	902	16.00%	30.10%	53.90%
CKD	1238	347	525	58.70%	16.40%	24.90%
COPD	783	392	866	38.40%	19.20%	42.40%
Cirrhosis	991	2290	627	25.40%	58.60%	16.00%
Depression	5016	659	354	83.20%	10.90%	5.90%
Neurologic disorder	1882	521	1475	48.50%	13.40%	38.00%
Alcohol disorder	1026	447	58	67.00%	29.20%	3.80%
Remaining costs	1	1	1	33.30%	33.30%	33.30%
Death costs	1	1	1	33.30%	33.30%	33.30%

Of interest are the proportions in the last 3 columns. As one can see, for acute conditions such as strokes, MI, cancer and depression, inpatient costs indeed account for a large proportion of total medical costs. On the other hand, for diseases that are more chronic in nature, such as diabetes and COPD, pharmaceutical component plays a greater role. For simplicity (and due to the lack of information), we assumed that the differentials in residual and death-related costs between countries were equally driven by the differentials in the three separate components: Inpatient, Outpatient, Pharma. In addition, we assumed that in the first year of diagnosis, the differentials in more acute conditions such as strokes, MI and cancer, were driven entirely by the differentials in hospitalization costs. In the subsequent years, we assumed the weights given in Tables 4 and 5 for all conditions.

For the Central/Eastern EU regions, we used the weights estimated using the SHA OECD data for Hungary:

Table 4.3. Treatment component weights by disease, Hungary (for Central/Eastern EU region extrapolation)

	Inpatient	outpatient	pharma	Inpatient, %	Outpatient, %	pharma, %
Ischemic stroke	106439	37635	155082	35.60%	12.60%	51.80%
Haemorrhagic stroke	106439	37635	155082	35.60%	12.60%	51.80%

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MI	106439	37635	155082	35.60%	12.60%	51.80%
Cancers	59426	10315	59411	46.00%	8.00%	46.00%
Diabetes	10506	10325	77951	10.60%	10.50%	78.90%
CKD	24620	10859	18370	45.70%	20.20%	34.10%
COPD	32963	16575	44632	35.00%	17.60%	47.40%
Cirrhosis	32435	32154	36641	32.00%	31.80%	36.20%
Depression	29783	12733	40703	35.80%	15.30%	48.90%
Neurologic disorder	14500	5223	23907	33.20%	12.00%	54.80%
Alcohol disorder	32647	12219	5780	64.50%	24.10%	11.40%
Remaining costs	1	1	1	33.30%	33.30%	33.30%
Death costs	1	1	1	33.30%	33.30%	33.30%

Finally, conversion weights were estimated according to formula 11, and are shown below for the Southern region (Table 4.5) and for the Central/Eastern region (Table 4.6).

Table 4.4. Conversion factors from France to Southern region (weights based on Dutch SHA data)

	Italy	Portugal	Greece	Malta	Slovenia	Spain	Cyprus	Croatia
Ischemic stroke	0.668	0.407	0.508	0.508	0.462	0.603	0.508	0.508
Haemorrhagic stroke	0.668	0.407	0.508	0.508	0.462	0.603	0.508	0.508
MI	0.668	0.407	0.508	0.508	0.462	0.603	0.508	0.508
Cancers	0.665	0.383	0.508	0.508	0.454	0.58	0.508	0.508
Diabetes	0.683	0.528	0.507	0.507	0.507	0.72	0.507	0.507
CKD	0.665	0.402	0.512	0.512	0.462	0.602	0.512	0.512
COPD	0.669	0.444	0.515	0.515	0.479	0.645	0.515	0.515
Cirrhosis	0.723	0.654	0.462	0.462	0.533	0.806	0.462	0.462
Depression	0.658	0.341	0.511	0.511	0.44	0.542	0.511	0.511
Neurologic disorder	0.661	0.402	0.52	0.52	0.466	0.607	0.52	0.52
Alcohol disorder	0.683	0.453	0.49	0.49	0.472	0.634	0.49	0.49
Remaining costs	0.688	0.52	0.496	0.496	0.499	0.703	0.496	0.496
Death costs	0.688	0.52	0.496	0.496	0.499	0.703	0.496	0.496

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Table 4.5. Conversion factors from Estonia to the other countries in Eastern/Central region (disease weights based on Hungary SHA data).

	Bulgaria	Poland	Romania	Slovakia	Hungary	Latvia	Lithuania
Ischemic stroke	1.335	1.092	1.335	1.562	1.335	0.833	0.833
Haemorrhagic stroke	1.335	1.092	1.335	1.562	1.335	0.833	0.833
MI	1.335	1.092	1.335	1.562	1.335	0.833	0.833
Cancers	1.322	1.13	1.322	1.546	1.322	0.815	0.815
Diabetes	1.472	1.053	1.472	1.736	1.472	0.944	0.944
CKD	1.225	1.083	1.225	1.42	1.225	0.753	0.753

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COPD	1.297	1.072	1.297	1.512	1.297	0.81	0.81
Cirrhosis	1.197	1.012	1.197	1.381	1.197	0.749	0.749
Depression	1.312	1.082	1.312	1.532	1.312	0.818	0.818
Neurologic disorder	1.351	1.09	1.351	1.582	1.351	0.846	0.846
Alcohol disorder	1.102	1.103	1.102	1.264	1.102	0.658	0.658
Remaining costs	1.178	1.008	1.178	1.357	1.178	0.736	0.736
Death costs	1.178	1.008	1.178	1.357	1.178	0.736	0.736

4.5. OTHER Modelling issues

4.5.1. General issues

Due to the data constraints, for individuals before the age of 18, all the costs are assumed to be zero. This is not likely to be a major concern because we are interested in modelling the costs for diseases that have very low prevalence in these age groups (this was also clear from the disease prevalence graphs we referred to, earlier).

In general, we used cost estimates split by two broad age groups: 18-65 and 65+ years, to ensure that we have sufficient sample size for parameter estimation. We have made the exception for myocardial infarction, breast cancer, diabetes, COPD and depression, using the narrower age groups (18-39; 40-49; 50-59; 60-64; 65-69; 70-74; 75-79; 80-84; 85-89; 90). This was made possible by the larger sample size owing to greater than 1% prevalence of these conditions in the population.

Because of the data limitations, when a person is modelled to have 3 or more conditions, the costs for only 2 are included in the model: the main one (always the most recent) and the comorbidity, i.e. the latest previous one not being in the same disease group (e.g. another cancer or stroke type). When two diseases have thus been assigned a role, the model will keep this arrangement until the occurrence of a new condition, which will become the “main one”.

For the people who died, in the last year of life, we assumed that they will accumulate only half of their extra residual and disease costs.

The residual costs are bound to the original selection of diseases for FRESHER. While the model can run with a reduced selection of diseases, the total predicted costs would be under-estimated in this case.

When estimating the regional tables, the region-specific cost of disease was calculated as the weighted average of the country-specific costs of disease (where weights are country population sizes ratios by age and gender).

The costs of some of the FRESHER-modelled conditions (e.g. back pain, injuries) were impossible to estimate with the administrative data. They will be estimated separately using a different methodology.

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4.5.2. Issues specific to France

The study population is all persons aged 18 or older on January 1st 2014, sampled in the EGB database and alive on December 31st 2014.

In the EGB database for France, three types of data can be used to identify patients with diseases:

1. The Affection de Longue Durée (ALD) registry
2. The drug prescription database (pharmacy data from le Système national d'information inter-régimes de l'Assurance maladie (SNIIRAM))
3. Hospital discharge data (PMSI)

For more information regarding the disease identification methodology, consult (Cortaredona and Ventelou, 2017[10])

The outcome variable is the total cost of hospital and ambulatory care in 2014 (annual amount reimbursed by the National Health Insurance) calculated at the patient level. The following costs are included in the French analysis: primary care and consultations with specialists, (reimbursed) medicines, medical procedures, biological tests, medical devices, emergency care and hospital inpatient care. This pricing of ambulatory care also takes into account possible copayment from the patient, except for over-the-counter drugs which are not available in the EGB database. However, in France, almost all costs for the long-term chronic conditions such as those we are considering (especially those identified as ALD in the LTI database) are almost completely covered by the social security system. Therefore, there are hardly any OOP/other costs not taken into account in the estimation. For more details about the different components as mentioned above, refer to (Cortaredona and Ventelou, 2017[10]).

Regarding the hospital sector, this cost estimation only takes into account the part of cost which is reimbursed to hospital through the diagnosis-related group (DRG) payment system (through which we can clearly assign a diagnosis using the reason of admission). DRG rates were used as proxies of case costs for public and private not-for-profit hospital stays. All other costs supported by the hospitals are not included, such as mission of general interest, clinical research, exploitation deficit.

4.6. Issues specific to Estonia

The sample in Estonia is restricted to the users of health care, and therefore excludes healthy people; people with undiagnosed FRESHER and other chronic conditions; and patients with diagnosed FRESHER or other conditions that did not use any healthcare (e.g. not even visiting a doctor for a brief consultation). This is an excerpt from Estonia report (Thiébaut, 2017[12]):

In Estonia, 95% of the population…is covered by a mandatory public insurance while private insurance is almost non-existent. The public health insurance is financed through a solidarity-based mandatory contributions in the form of an earmarked social payroll tax collected by the Estonian Health Insurance Fund (EHIF), an independent public institution. EHIF is the main purchaser of health care (HC) in Estonia… The dataset is an extract from EHIF discharge database, it contains all reimbursement costs for primary

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care, specialists, hospital stays and rehabilitation claimed to EHIF by each Estonian people who have used the HC system during the year 2013…

After removing missing cases and people under 18 years old, 817 522 individuals were available for analysis.

EHIF reimbursement dataset was combined with the Estonia Census to make it more representative of the whole population. The predicted costs E(C|C>0, disease=1) and E(C|C>0, disease=0) were representatives of the users of healthcare. To make them representative of the whole population, such costs were multiplied by P(C>0) using logit parameters estimated on the combined EHIF and Census sample. Otherwise, the approach was similar to the one described in the second part of this paper.

Primary care in Estonia is financed by capitation system: family doctors are practicing on the basis of a list of enrolled patients for whom they receive an annual capitation payment from EHIF. As a result reimbursement costs for primary care reported into EHIF claims file are very small, and often equal to zero (i.e.: GP's visit are "free" for every Estonian person enrolled). A high proportion of patients in EHIF sample had zero reimbursed costs but were nevertheless users of healthcare. In such cases, individual cost has been corrected by computing an implicit cost of GP's visit valued at 9.14 Euros, which were added to each bill for family medicine visits.

The claim file does not contain individual medication consumption. However EHIF accounts provides annual prescribed medicine cost compensated by EHIF: 112 793 thousands Euros in 2013. Knowing total EHIF claimed reimbursement from our dataset is equal to 490 740 thousands Euros, we compute a ratio of prescribed medicine as share of EHIF reimbursed cost: 112 793 / 490 740 = 0.23, or pharmaceuticals cost = 0.23 times observed reimbursed cost. We apply this factor to each bill amount to get individual prescribed medicine cost.

Table 3 in report by (Thiébaut, 2017[12]) presents distribution of OOP expenditure highlighting main components: prescribed and OTC medicines, dental care, specialists outpatient, LTC, glasses, and outpatient rehabilitation. OOP for prescribed medicines was differentiated by disease group according to table 11: previously estimated prescribed medicine cost is multiplied by OOP/EHIF ratio according to NCD identified as main diagnosis for visit/stay using diagnosis sequence variable. Other OOP components were not included (OTC, LTC, glasses and dental care).

Since the time since diagnosis is not defined in the EHIF dataset, we assume that the average extra disease costs apply at all years since diagnosis. Therefore, when extrapolating the costs from Estonia to the other countries in Eastern/central EU region, we always used the conversion factors provided in Table 4, including for acute conditions such as strokes, MI and cancer. Because of the data limitations, the disease groups are different in Estonia compared to France. Specifically, the costs were estimated for the following disease categories:

- AMI
- Alcohol use
- Cancers
- Strokes
- Cirrhosis

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- CKD
- COPD
- Depression
- Diabetes
- Neurological disorders
- Residual costs

For more information, refer to (Thiébaut, 2017[12]).

4.6.1. Issues specific to the Netherlands (work ongoing)

Since 2006 reform, Dutch citizen are covered by mandatory private insurance while public insurance no longer exists. The government continues to play a regulation role and subsidizes premiums among the low-income population.

The COI analysis was performed on 2013 reimbursement cost database of the main private insurer named Vektis who is in charge to collect all discharge data from every Dutch insurer. This leads to 98% of cost coverage and 95% of population representativity. The 2% of remaining cost are OOP: this cost component was corrected at individual level according to age and gender (see (Thiébaut, 2017[12])for more details).

4.7. Preliminary validation

In Table 20, we compare total medical costs predicted using our model with the costs from the SHA dataset (OECD). The first column contains our model prediction; the second- the total health expenditures from the SHA, for curative healthcare, together with rehabilitation and primary healthcare expenditures. Finally, in the third column, we show SHA estimates which also add medical goods spending to the second column numbers.

The first three countries in the table belong in Eastern European region. As the data at the moment does not take into account out of pocket expenditures (mostly drugs), it's not surprising that the costs in Estonia and two other countries in this region tend to be lower than the costs in SHA columns. However, the magnitude of the difference does not appear to be too large. The OOP expenditures will be taken into account in the final model version.

On the other hand, the costs are quite close in 1st and 3rd columns for Italy, Portugal and Slovenia. Our prediction is considerably lower for Greece than the corresponding number from SHA data, but it's important to keep in mind that there was a large drop in financing in Greece during the last few years. In fact, in 2010, financing in Greece was not very much different from the one predicted in our model. The fact that the cost in France predicted in our model (118.8) is quite close to the one in the second column (114.1) but also quite different from the one in the 3rd column (144.1) can be due to the fact that "medical goods" category includes not only drug spending, but also a range of medical devices which may not be covered by the French administrative dataset. Therefore, such costs can be underestimated for the residual cost component. The differential may also be partly due to the fact that the data on the OTC spending is not completely available in the French dataset. Moreover, the EGB dataset only takes into account the part of hospitalization costs which are reimbursed to hospital through the diagnosis-related

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group (DRG) payment system (through which a diagnosis at admission can clearly be assigned). All other costs supported by the hospitals are not included, e.g. mission of general interest, clinical research, exploitation deficit, etc. Finally, at the moment not all diseases are modelled in Fresher.

Table 4.6. Predicted total cost comparisons by country, in Euros, current prices, 2014

Country	Model prediction	SHA*	SHA**	SHA***
Slovakia	1.91	2.38	2.5	3.633
Estonia	0.37	0.58	0.6	0.735
Latvia	0.44	0.41	0.4	0.57
France	118.8	111	114.1	144.1
Italy	86.6	67	72.4	88.4
Portugal	10.4	7.7	7.8	9.302
Greece	10.9	4.97	5.2	7.39
Slovenia	1.96	1.42	1.5	1.804
Spain	61.4	40.8	42.7	53.23

Note: *curative &rehabilitative care; ** curative, rehabilitative and primary care; *** curative, rehabilitative, primary care and medical goods

5. Scenarios from global trends

5.1. Modelling framework

Four scenarios have been associated with evolving trends in the main risk factors for chronic diseases, based on the evaluations of health experts (see Deliverables 4.2 and 5.2 of the FRESHER project, for detailed methodology on this qualitative-quantitative exercise). For every risk factor, experts were only asked to give their views on one parameter (e.g. prevalence of obesity for BMI) for the all Europe. We then have to make some assumptions in how those trends translate in the three different zones and in the full distribution of the risk-factors.

1. **No convergence in Europe, the gaps remains constant**. We have assumed that the differences in prevalence of risk factors between the geographical zones remain the same at horizon 2050. The three zones follow parallel trends.

2. **No demographic effect included in expert views.** We have assumed that the experts gave their views with an age standardize perspective. In practice we have keep the population distribution of 2015 to compute the adjustment on the risk factors' distributions.

3. **Constant absolute spread over age.** In most of risk factors (except tobacco) prevalence rises with age. We have assumed that all age categories contribute equally to the trend and then we have decided to shift all the distributions by age with the same absolute shift.

4. **Linear trend from 2015 to 2050.** We have assumed Europe is reaching the expert views in 2050 on a linear trend.

5.2. Methodology by risk factor

5.2.1. Alcohol

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We keep the prevalence of current drinker constant. We shift the average alcohol daily intake (g/day) to make the expert views. The gamma distribution, modelling alcohol consumption, is then automatically updated as explained in 3.2.4.2.

5.2.2. BMI

For BMI, experts only gave their view on the evolution of the prevalence of obesity. As explained in 3.4, we model BMI through the prevalence of 7 different categories of BMI. We then have to translate the shift into those 7 categories.

We have assumed that categories above obesity will be uniformly shifted to match the desired obesity level. Then we assume the prevalence of strictly overweight (BMI between 25 and 30) do not change over time. And we assume that the categories of normal weight compensate the raise of obesity. We based this hypothesis on our input data as you can see in the table below

Table 5.1 Evolution of the prevalence of the different categories of BMI in France (for age 50-55)

	Female Normal weight	Overweight	Obesity	**Male** Normal weight	Overweight	Obesity
Between 1990 - 1995	-6%	2%	-6%	-10%	1%	14%
Between 1995 - 2000	-7%	1%	-7%	-11%	0%	14%
Between 2000 - 2005	-7%	1%	-7%	-12%	0%	13%
Between 2005 - 2010	-7%	1%	-7%	-10%	-1%	11%
Between 2010 - 2014	-6%	0%	-6%	-8%	-1%	7%

5.2.3. Blood Pressure

As explained in 3.3, blood pressure is modelled with a log normal distribution. We then assume that the standard deviation remains constant, we only shift the average systolic blood pressure.

5.2.4. Physical Activity

We shift the prevalence of inactivity; the other categories compensate the increase (or the decrease) in a uniform way.

5.2.5. Smoking

We shift the prevalence of smokers and the prevalence of non-smoker as well in the opposite direction.

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6. Modelling interventions

6.1. General principles

On top of scenarios, which define the trends for demography and epidemiology at global level, the microsimulation model uses interventions to modify the life trajectory of individuals. They can be used to transform most of the aspects of the simulation, but in FRESHER they are essentially used to reflect the impact of a prevention policy on risk factors of individuals.

6.2. Specifications

Among the most effective interventions to tackle the main risk factors linked to NCDs (smoking, alcohol, obesity), we have selected one reference intervention for each risk factor.

6.2.1. Smoking

The intervention selected as the most effective one to reduce smoking is the taxation of tobacco.

6.2.1.1. Tobacco taxation

Characteristics

Based on ISS's review of quantitative evidences on effectiveness of policy option to tackle tobacco smoking (Hopkins, Briss et al. 2001) and((CPSTF))

- **Elasticity**: -0.37 for young people up to age 24, -0.18 for adults 25+
- **Effect:** we have used a taxation rate of 20 %
- **Efficiency over time:** full effect reached immediately when the intervention begins, lasts forever

Model definition

```
SmokingReduction --begindate 2018-01-01 --factor 20 --effect 24:-0.37&25:-0.18 --efficiency 0:100
```

6.2.2. Alcohol

The intervention selected here is a combination of alcohol advertising regulation and taxation.

6.2.2.1. Alcohol advertising regulation

Characteristics

Based on OECD's report on impacts of alcohol policies (Cecchini, Devaux and Sassi, 2015[6]) . Only the effect on binge drinking has been used here (the effect on consumption being affected by the taxation).

- **Effect**: -1.6 % of binge drinkers in the whole population
- **Efficiency over time**: linear increase (full effect reached after 1 year), lasts forever

6.2.2.2. Alcohol taxation

Characteristics

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Based on OECD's report on impacts of alcohol policies (Cecchini, Devaux and Sassi, 2015[6]). Each elasticity value represents the mean of a normal distribution (sigma = |mu| / 2) used to randomly draw the effect for a given individual in the corresponding drinking category.

- **Effect** : we have used a taxation rate of 10 %
- **Efficiency over time**: full effect reached immediately when the intervention begins, lasts forever

Table 6.1 Price elasticity according to drinking category

Age	Female not harmful	Female harmful	Male not harmful	Male harmful
≤ 24	-0.42	-0.24	-0.29	-0.17
25-59	-0.06	-0.35	-0.42	-0.24
≥ 60	-0.59	-0.34	-0.41	-0.24

6.2.3. Obesity

The intervention selected as the most effective here is the tailored counselling by GP or dietetician, targeting overweight or obese individuals.

6.2.3.1. Obesity Counselling

Characteristics

Based on THL's review of quantitative evidences on effectiveness of policy option to tackle obesity (Booth et al., 2014[13]).

- **Effect** :
  - after 1 year : -1.36 kg translating to -0.47 kg/m² assuming an average size of 1.70 m
  - after 2 years : -1.23 kg translating to -0.42 kg/m² (which represents 90% of -0.47)
- **Efficiency over time**:
  - linear increase, maximum effect reached after 1 year
  - then linear decrease to 90 % after 2 years
  - then stay at 90 % forever

6.3. Policy package

We have combined three interventions in one policy package, see deliverable 5.2. We assume that the effect of the three policies are independent and do not interact which each other.

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7. Appendix

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Table 7.1 IHME nature of injury and associated short/long term disability weight(Vos, Allen et al. 2016).

Id	IHME nature of injury	Health State Short Term	GHE 2015	Health State Long Term	GHE 2015
N1	Open wound, superficial injuries and dislocations	Open wound: short term	0.006		
N2	Injury Requiring Urgent Care	Poisoning: short term	0.132		
N3	Injury Requiring Emergency Care	Drowning and non-fatal submersion: short or long term	0.247	Drowning and non-fatal submersion: short or long term	0.159
N4	Fracture of clavicle, scapula, humerus, or skull	Multiple	0.053	Multiple	0.053
N5	Fracture of sternum, rib, or face bone	Multiple	0.085	Multiple	0.067
N6	Fracture of wrist and other distal part of hand, fracture of foot except ankle	Fracture of hand: short term	0.01		
N7	Fracture of radius or ulna	Fracture of radius or ulna: short term	0.028		
N8	Fracture of femur	Fracture other than neck of femur: short term	0.111		
N9	Fracture of Hip	Fracture of neck of femur: short term	0.258		
N10	Fracture of patella, tibia, fibula, or ankle	Fracture of patella, tibia or fibula, or ankle: short term	0.05	Fracture of patella, tibia or fibula, or ankle: long term	0.055
N11	Fracture of pelvis	Fracture of pelvis: short term	0.279	Fracture of pelvis: long term	0.182
N12	Long term outcome of dislocation of hip/knee/shoulder			Multiple	0.0637
N14	Burns, <20% total burned surface area without lower airway burns	Burns of <20% total surface area without lower airway burns: short term	0.141	Burns of <20% total surface area or <10% total surface area if head or neck, or hands or wrist involved: long term	0.016
N16	Burns, ≥ 20% total burned surface area or ≥ 10% total burned surface area if head/neck or hands/wrist involved	Burns of ≥20% total surface area: short term	0.314	Burns of ≥20% total surface area or ≥10% total surface area if head or neck, or hands or wrist involved: long term	0.135
N17	Amputation of both lower limbs or both upper limbs			multiple	0.1055
N19	Amputation of one lower limb or one upper limb			multiple	0.0785
N20	Amputation of finger(s) (with or without thumb or toe)			multiple	0.008
N21	Injured nerves	Injured nerves: short term	0.1	Injured nerves: long term	0.113
N22	Spinal cord lesion at neck level			Spinal cord lesion at neck: treated	0.589
N23	Fracture of vertebral column	Fracture of vertebral column: short or long term	0.111	Fracture of vertebral column: short or long term	0.111
N24	Spinal cord lesion below neck level			Spinal cord lesion below neck: treated	0.296
N27	Severe of traumatic brain injury	Severe traumatic brain injury: short term	0.11	Traumatic brain injury: long-term consequences, severe	0.637
N28	Severe chest injury	Severe chest injury: short term	0.369	Severe chest injury: long term	0.047

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Table 7.2 IHME prevalence of the different "nature of injuries" in the cause injuries (Vos, Allen et al. 2016)

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N14	N16	N19	N20	N21	N22	N23	N24	N25	N26	N28
Road injury	1.8%	3.2%	6.9%	7.9%	2.0%	3.6%	2.1%	4.9%	11.9%	2.7%	1.5%	0.1%	0.5%	0.1%	0.1%	0.2%	0.6%	4.5%	0.3%	2.1%	11.7%	12.4%	1.8%
Falls	3.1%	0.9%	8.3%	4.7%	2.4%	6.2%	2.7%	17.2%	11.2%	1.8%	2.4%	0.0%	0.5%	0.0%	0.0%	0.1%	0.4%	5.7%	0.4%	0.9%	9.1%	6.0%	3.1%
Drowning	3.8%	64.8%	1.2%	1.8%	0.1%	0.5%	0.8%	1.4%	2.1%	0.3%	0.7%	0.2%	0.7%	0.0%	0.0%	0.1%	2.6%	3.0%	0.4%	0.5%	3.9%	2.8%	3.8%
Self-Harm	72.3%	2.7%	0.7%	1.2%	0.4%	0.3%	0.3%	0.3%	0.6%	0.3%	0.0%	1.0%	0.5%	0.0%	0.1%	0.6%	0.0%	0.5%	0.2%	0.0%	1.0%	2.5%	72.3%
Interpersonal violence	8.9%	4.9%	5.8%	13.2%	1.3%	1.8%	0.5%	1.7%	1.8%	0.3%	0.5%	0.7%	1.3%	0.0%	0.1%	0.8%	0.2%	1.2%	1.5%	0.3%	11.7%	4.2%	8.9%

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