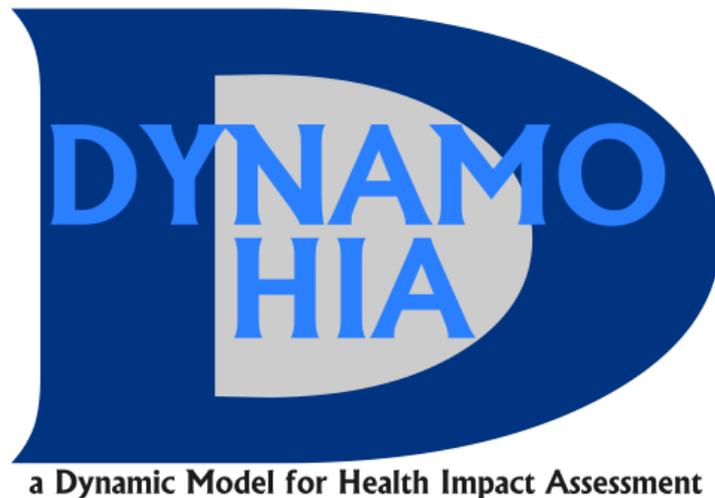


DYNAMO-HIA
DELIVERABLE D1
MODEL SPECIFICATION FOR A DYNAMIC MODEL
FOR HEALTH IMPACT ASSESSMENT

15th July, 2008



Stefan K. Lhachimi
Wilma J. Nusselder
Pieter van Baal
Hendriek Boshuizen
Sido Mylius
Jet Smit

A prior version of this document was discussed at the DYNAMO-HIA expert meeting on May 23rd, 2008, in Rotterdam.

Executive Summary

Background and Objectives

DYNAMO-HIA i) develops a dynamic modeling tool to quantify the health impact of policies by comparing a projected reference scenario with a projected intervention scenario and ii) applies it to selected life-style related health-determinants and resulting diseases across EU countries. The tool has public health practitioners as its target audience and will be made publicly available. DYNAMO-HIA is funded by the Public Health Executive Agency (PHEA) as part of the EU Public Health Program 2003-2008 of the European Commission's Directorate General for Health and Consumer Affairs (DG SANCO), with co-financing from the Erasmus Medical Center Rotterdam, the Institute of Public Health and the Environment in the Netherlands, the Catalan Institute of Oncology, the International Obesity task force, the London School for Hygiene and Tropical Medicine, the Haughton Institute in Dublin, and the Istituto Tumori in Milan. In summary, this three year project (commenced in May 2007) will:

-
- develop a quantitative modeling methodology to estimate the health impact of policies that change health determinants and implement this in a stand-alone software (DYNAMO-HIA)
 - compile and make available data sets (consistent across EU countries) on a few example risk factors (smoking, obesity, and alcohol consumption) and their effects on four example diseases (cancer, cardio vascular disease (CVD), diabetes, and chronic obstructive pulmonary disease (COPD)) in the European Union and thus provide ready-for-use data for these determinants and diseases
 - illustrate the tool by assessing the health effects of several health-relevant policy options with regard to these health determinants

Model

The tool aims to facilitate quantitative health impact assessment (HIA). An HIA compares the population health impact of one or more policy interventions with a baseline scenario. However, no satisfactory simulation tool exists that can be used to quantify the effect of changes in health determinants, resulting from a policy change, on health outcomes. The DYNAMO-HIA tool – which intends to fill this gap – has to strike a balance between being i) a sufficiently realistic formal model, ii) user friendly, and iii) able to accommodate commonly available epidemiological data to ensure wide applicability. To reconcile these multiple targets, we developed a set of desiderata and constraints to evaluate existing models and guide the development of the new tool. Hence,

the specification process was based on existing models (such as PREVENT, ARMADA, or RIVM-CDM) and focused on synthesizing already established features.

DYNAMO-HIA will be a *dynamic simulation* model with *discrete* time steps in 1-year intervals. The *population heterogeneity* will allow differentiation according to sex, age, risk factor, and disease. DYNAMO-HIA will feature a general *disease model* (allowing to model *multiple* chronic diseases) and is based on a multi-state modeling approach. The tool models *explicit* risk factor states and hence allows for *mortality selection*. Apart from health determinants (e.g. life style related or environmental risks), *diseases can be risk factors* for other diseases. The model will mainly need *standard epidemiological data* such as disease incidence, prevalence, mortality, and relative risks (by sex and age).

Risk factors can come in three different forms: *continuous*, in *classes* (up to 9 categories), and in classes where *duration of class membership* is important. The model is envisioned to accommodate up to three different disease process: *chronic diseases*, *partly acutely fatal diseases*, and diseases where the excess mortality depends on the *duration of the diseases*. The policy induced change in risk factor prevalence or risk factor transition rates will be determined by the user. Hence, the tool can be used after the user has specified the effect of policies on health determinants. Several population based health *outcome measures* (such as life expectancy or DALE) will be readily available to quantify the difference between the reference and the different policy scenarios. The suggested prediction span is about 10 to 15 years.

Data on Risk Factors and Diseases

The second part of the project is to derive and make publicly available internally consistent incidence, prevalence and disease mortality (IPM) data by age and sex for the example diseases. Furthermore, data on risk factor prevalence and relative risks quantifying the association between the example risks factors, the example diseases, and total mortality are collected. Those data will be ready to use with the developed software. The risk factors are obesity, alcohol consumption, and smoking. The diseases are cardiovascular diseases and diabetes, chronic obstructive lung disease (COPD), and (selected) cancer sites.

The collected data will be compiled from already existing data sources. It is intended – depending on availability – to collect these data for each EU member state. The covered time span used as the baseline for the data collection is between 2000 and 2006. To achieve more stable estimates the data of several calendar years might be pooled. Stable and internally consistent data are of great importance for a dynamic model as the errors propagate with each simulated time step.

Future Steps

After the first expert meeting, the model specification will be finalized and the technical model will be implemented in a software, with a special emphasis on user friendliness. Moreover, input data for the tool will be compiled. With the

completed tool and the example datasets a number of instructive scenarios for practical health policy interventions will be simulated. The final model and the accompanying data sets will be launched during the second expert meeting (including a training seminar) in 2010. The software will include an extensive manual that – inter alia – gives advice on how to construct policy scenarios (e.g. illustrative examples, how to conduct sensitivity analysis etc).

Work Packages

The DYNAMO-HIA consists of 11 work packages:

1. Coordination of Project
Johan Mackenbach, Wilma Nusselder, Jet Smit
2. Dissemination of the Results
Jet Smit
3. Evaluation of the Project
Johan Mackenbach
4. Model Specification
Wilma Nusselder, Stefan Lhachimi
5. Construction of Software Tool
Hendriek Boshuizen, Sido Mylius, Pieter van Baal
6. Smoking
Estevez Munoz
7. Overweigh/Obesity
Tim Lobstein, Rachel Jackson-Leach, Philip James
8. Alcohol
Martin McKee, Joceline Pomerleau, Kate Charlesworth
9. CVD and diabetes
Kathleen Bennett, Simon Capewell, Julia Critchley, Bernie McGowan
10. Cancer
Andrea Micheli, Paolo Baili, Camilla Amati, Ilaria Casella, Natalia Sanz
11. Definition of Scenarios and COPD
Wilma Nusselder, Stefan Lhachimi, Margarete Kulik

Contents

Executive Summary	iii
1 Overview	1
2 Health Impact Assessment	3
2.1 Background	3
2.2 Objectives of HIA	5
2.3 HIA-based Model Requirements	6
2.3.1 Desiderata for an HIA-Tool	7
2.3.2 Constraints an HIA-Tool faces	10
2.3.3 Bringing together Desiderata and Constraints	11
2.4 Validity in HIA	13
2.5 Review of Selected Computer Simulations used for HIA	15
3 Computer-Based Simulations	21
3.1 Terminology of a Computer Simulation	22
3.1.1 Functional Elements	22
3.1.2 Variability, Heterogeneity, and Uncertainty in Decision Models	26
3.2 Common Modeling Approaches in HIA	28
3.3 Multi State Modeling of Chronic Diseases	32
3.4 Embedding the Policy Effect	37
3.5 Evaluation of HIA Simulations: Validity and Uncertainty	39
4 DYNAMO-HIA	43
4.1 Proposed Model Specification	43
4.2 Achieving Validity	48
5 Technical Outline of DYNMAO-HIA	51

CONTENTS

6	Appendix A: Overview of Collaborating Partners and Consulted Experts	62
7	Appendix B: Review of Existing Models	66
7.1	Search Strategy	66
7.2	Evaluating Existing Models	67
7.3	Vignettes for Selected Models	71
7.3.1	ARMADA	71
7.3.2	Multi State Life Table (MSLT)	74
7.3.3	POHEM	77
7.3.4	Foresight Obesity Project	79
7.3.5	PREVENT	82
7.3.6	RIVM-CDM	84
7.4	Background on further Reviewed Models	89
	Bibliography	105

Section 1

Overview

The objective of this document is to outline the specification process for a *Health Impact Assessment* (HIA) tool within the DYNAMO-HIA project. A *tool* in this context is a piece of computer software being able to simulate different policy proposals and their effects on population health via changes in risk factor exposure. In the context of quantitative HIA, a tool compares a projected reference scenario with a projected intervention scenario. The focus of such models is to quantify the effect of a policy on net population-health, not the prediction of future population health as such. Based on a set of criteria derived from the objectives of HIA, we conclude that no available software is able to do so sufficiently; however, many interesting features and insights about constructing such a tool can be gained from the already existing literature.

In section 2, we outline briefly the setting and the objectives of an HIA exercise. From this starting point, we develop seven criteria to evaluate existing

SECTION 1. OVERVIEW

HIA tools and guide the development of the new DYNAMO-tool. Furthermore, we outline three constraints that have to be taken into account when designing a new tool. Then, we outline principles of validity within a quantitative HIA exercise. Finally, we give an account of a number of already existing models, that guide us in the design process.

In section 3, we give some background information about computer simulations. It starts with a brief review of the basic technical choices for computer simulations. Then an overview about the main simulation approaches taken in HIA is given. Next, we introduce multi state models (MSM) for simulating chronic diseases. The section concludes with some considerations concerning the modeling of policies and on how to achieve validity in a computer simulation.

In section 4, we propose the model specification for the DYNAMO-tool. This is a non-technical description based on the considerations made in the previous sections. In section 5 the preliminary technical outline of the DYNAMO-tool is presented. In the appendix (section 7) an overview of the reviewed models is given, including search strategy and vignettes of selected models.

Section 2

Health Impact Assessment

2.1 Background

The most widely used definition stems from the Gothenburg consensus paper and states HIA is 'a combination of procedures, methods, and tools by which a policy, program, or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population. [World-Health-Organization 1999].

HIA is a multi stage process divided into the following steps [Project-Group 2004; Mindell et al. 2003; Parry et al. 2005; Cole and Fielding 2007]:

- Screening
- Scoping
- Effect Analysis
- Reporting of Findings

- Monitoring and Evaluation

A quantitative HIA-tool compares two or more policy options and quantifies the difference in the projected health outcomes. This is done in the stage of *effect analysis* and consist of three different tasks that an HIA tool has to address:

- Description of the baseline situation
- Estimation of change in exposure to determinants of health
- Estimation of change in health outcomes

To estimate the change in health outcomes from the change in exposure to determinants of health, quantitative models are needed (see Figure 2.1 for a conceptual overview and role of a quantitative tool).

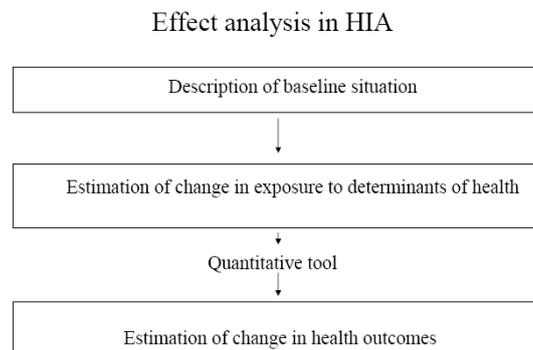


Figure 2.1: Conceptual overview of effect analysis and role of a quantitative tool

2.2 Objectives of HIA

An HIA exercise usually has three main objectives. First, to *predict* the impact of a policy¹, second, to allow *participation* of stakeholders in the assessment process, and, third, to *inform* the decision making process [Parry et al. 2005].

The first objective is closest to epidemiological considerations. The causal pathway(s) by which the policy affects health have to be identified. This is done through risk factor exposure (the determinants of health). When the causal structure is established, HIA aims to predict the health changes for the *whole* population and the distribution *within* the population. Not only the net effect is important, but also to identify winners and losers of a policy. It is necessary to be as thorough as possible and to identify the negative and the positive effects of the policy on health.

Some regard the second objective – to make the health assessment of a policy proposal a participatory endeavor – as the key feature of the HIA process. The main arguments are that residents have the right to be informed and are often the best source of information in an assessment. They know their community best and are the ones who are affected by the decision [Kemmer 2007]. Critics argue that it is onerous to motivate community members to participate and for larger projects it becomes impracticable. Certainly, for policy decisions at the national level it will be difficult to conduct an all-inclusive process [Parry and Wright 2003]. However, for every decision taken there are

¹The terms policy, project, proposal, and program will be used interchangeably.

different stakeholders with varying preferences involved and every HIA must accommodate their legitimate interests by being as transparent as possible.

Third, an HIA has to inform the decision making process with applicable knowledge. Just giving a plethora of (simulated) data or a simple yes /no answer will not be convincing in the policy arena. The derived information has to be put into an understandable and applicable form for the specific context. This objective stems partly from the practical observation that the assessment is normally done by different people than the actual decision taking. Although, HIA is becoming more and more common, many administrative units simply lack the adequately trained personnel to conduct an HIA [Lock and McKee 2005]. Furthermore, a policy process needs to have results in a timely fashion and the recommendations must be evidence based.

2.3 HIA-based Model Requirements

From the setting and objectives of an HIA process some criteria can be postulated that a quantitative HIA tool has to fulfill. Some criteria are binary and some can be thought along a continuum of maximization or minimization. But the development of a tool also faces constraints. These stem from different sources: partly from the nature of the HIA process, partly from pragmatic considerations as resources to implement and utilize such a tool are limited. Furthermore, certain constraints have to be taken into account as well.

2.3.1 Desiderata for an HIA-Tool

First, the tool has to be *publicly available*.² As HIA is a democratic/participatory process, different stakeholders must have the opportunity to verify the results for themselves and test policy-scenarios of their own liking. Furthermore, a publicly available tool is open to peer review by the academic community. As a result it increases the trust a user can have in the simulated outcomes.

Second, the tool must be able to accommodate *heterogeneous populations*. An increased net-health gain on the population level is questionable when some members will be worse off. Certainly, a policy might be acceptable when a few suffer slightly and the majority of the population benefits. However, this has to be made explicit. It is important to identify the winners and the losers of a policy.

Third, the tool should be based on *epidemiological evidence* that can be inserted by the user in a form that is readily available from databases or from the epidemiological literature. The modeling of chronic diseases at the population level is usually done within the framework of multi state models (MSM) [Commenges 1999]. MSM are very flexible and allow the modeling of different (single and multiple) diseases within a population. Loosely speaking, two approaches for modeling the causal pathway of a disease process for a tool can be contrasted: a general health/disability model or a disease specific model. The former models directly the effect from a given risk factor prevalence in

²The order of the criteria does not reflect any order of importance.

the population on disability and mortality. The disease specific approach is an explicit modeling of the disease states: starting with risk factor exposure, the effect on disability and mortality is modeled via incidence and prevalence of the disease(s) in question. Furthermore, the effects of risk factor exposure on all-other mortality³ can be accounted for explicitly. The disease specific approach, despite its higher complexity, is to be preferred. Not only is epidemiologic evidence concerning the relationships between risk factor exposure and incidence and mortality richer and more reliable than for the former, it also allows to model the causal chain of the disease and hence yield more useful information.

However, the challenge in building such models is not primarily in specifying the MSM itself, but in the translation of the epidemiological evidence into transition rates as needed in these models. Epidemiological data such as incidence and mortality rates reflect the experience of an entire population, while such models require separate transition rates for different sub-populations, such as smokers and non-smokers, with or without a disease. The tool therefore should also provide the user with an implemented method to translate commonly available epidemiologic data into transition rates.

Fourth, the tool should be *dynamic*. Irrespective what exact epidemiologic model is chosen, the tool should be able to show the changes in population health over time. Not only the outcome matters, but also how and when it is reached. A long term health gain might be achieved by a health decrease in

³This becomes important if not all associated diseases are modeled and the risk factor affects other diseases as well.

the short run. Although this might be acceptable, it has to be identified and made explicit by an HIA tool.

Fifth, an HIA-tool should be *generic* in the sense that it could be used for different assessment exercises. The design and implementation of an HIA tool is a rather time consuming endeavor. Furthermore, it is for the user very onerous to get acquainted with a new model for every assessment. So it should be flexible enough to assess the effects of varying policy proposals and be able to model different diseases with varying risk factors.

Sixth, different kinds of *outcome measures* should be available. The tool intends to inform decision makers and given the decision at hand, different measures convey different meanings. Furthermore, different stakeholders might put different values on different measures. Several measures exist, such as life expectancy, prevented death, or health adjusted life expectancy. It is certainly open to discussion which outcome measures are more useful in which context, in particular as the choice might have ethical implications [Robberstad 2005; Gold et al. 2002]. However, the tool should be broad enough to satisfy the needs of different HIA exercises and stakeholders.

Seventh, a *general, real life population* should be simulated. In reality, populations differ tremendously in their age composition. As age does have an effect on most disease processes, a given change in risk factor exposure can yield different outcomes in different populations. A simple life table or a patient level population cannot model such differences. Furthermore, if longer time frames are used, the tool must be able to account for changes in the size

and the sex distribution of populations.

2.3.2 Constraints an HIA-Tool faces

Data availability – Every quantitative tool is limited by the data that is available to feed it. It is of limited use to build a very detailed model when there is virtually no data to use it. In the case of an HIA tool the data will be – most likely – annual and at the aggregated level differentiated by age and sex; although, in some instances more detailed data at the individual level derived from questionnaires might be obtainable.

Implementation – Every tool faces the risks of too much complexity. If a tool is too complex it might become too difficult to understand. In particular, it might become very onerous or impossible to establish formal validity (see 2.4). In general, parsimonious modeling is considered a virtue [Bratley et al. 1987]. Furthermore, more pragmatic reasons have to be considered: a complex model takes more time and resources to design, build, feed with data and most likely to communicate to a user. The former might be solvable given enough research funding. But the later should not be ignored light heartily. An HIA tool should be able to be used by a larger group of people than just the designers of the tool (see next paragraph). Hence, the used (disease) model has to strike the balance between realistic and simple.⁴

⁴One should note, that complex models usually have a lower predictive power than more simple models [Spielauer 2007].

Policy-User Side – Experts, such as the designer of a tool, often get carried away and lose sight of what reasonably can be expected [Brailsford 2005] from the user of a tool. However, the target audience should always be kept in mind.⁵ It is important to recall, that the tool has to satisfy the needs and the rationale of a policy arena. In this arena decisions often have to be taken under strong time pressure that does not allow to wait a longer period of time for "perfect" information.⁶ Hence, a tool has to aim to be able to yield results in a timely fashion.

It needs to be accessible enough that with sub-optimal resources (technical and human) the tool can be used and an analysis can be conducted. This translates roughly into a tool that should be usable with a standard personal computer and with a post-graduate education in the (public) health field.

2.3.3 Bringing together Desiderata and Constraints

Table 2.1 gives a cross tabulated overview about criteria and constraints pointing out the implications.

⁵This point is borderline between a constraint and a criterion as it is certainly a criterion to maximize user friendliness. But we decided to put it under constraints as to increase our awareness that the end-user should be the focus of all modeling undertakings.

⁶In this sense not taking an action or postponing it is a decision as well.

Table 2.1: Combined Overview of Criteria and Constraints

Implementation	Data Availability	Policy-User Friendliness
Publicly available	should not require additional commercial software	the required data should be (easily) available data entry should be clear and easy
Heterogeneous population	increasing heterogeneity increases complexity	increasing heterogeneity increases detail and applicability of predictions
Dynamic	making it dynamic increases complexity	more detailed time steps in simulation require more detailed time steps in data
Epidemiological model	Richer model increases complexity	richer model increases data needs the epidemiological model should be transparent
Generic model (easy to simulate different/multiple disease)	increases complexity	undetermined increases applicability
Outcome measures	increasing the number of outcome measures increases complexity	increasing the number of outcome measures increases applicability of predictions
Modeling general, real life population	increase complexity	increase data needs increases applicability of predictions

2.4 Validity in HIA

Every model is only as good as its ability to produce *valid* results. Validity, however, is a very broad concept; for applications in the field of HIA, Veerman et al. [2007] operationalizes validity by suggesting three different criteria:

- *plausibility* – the degree to which the theoretical framework of the tool is deemed to be understandable, applicable, and plausible by researchers, external experts, and stakeholders (this is sometimes also labeled *face validity*)
- *formal validity* – a tool should adhere to the rules of logic to reach its conclusions, the correct method should be applied in a correct way
- *predictive validity* – the predictions of a tool should be confirmed by the observed facts

The first criterion might seem vague at first sight, nevertheless, it is of utmost importance that a tool used in an open process such as HIA must be acceptable by all parties involved. This, of course, cannot mean it should be simplistic. But a competent person should be able to judge the appropriateness of the tool for the task at hand.

The second criterion is inherent to all research endeavors. It is interrelated to the first criterion but to be treated distinctive. Sometimes procedures are accepted despite the fact that their formal validity is not established. For a quantitative tool, however, this point is very important. It must be internally coherent to be able to produce valid and reliable results.

The last criterion can be considered the holy grail of HIA (or social sciences for that matter). Certainly, as an HIA makes predictions, a model that makes predictions is only truly valid when it is confirmed by the observed facts. A problem is that i) between prediction and observation of the true facts a long time lag exist, ii) an HIA might lead to a decision that alters the future in such a way that the originally predicted values might not be realized at all, and iii) a model is always a simplification of the reality, purposefully neglecting certain factors that have an influence. Hence, establishing "full" predictive validity within a social science/ behavioral setting is virtually impossible.⁷ Furthermore, in the case of an HIA exercise one usually compares a projection of the *reference* scenario with the projection of one (or more) *intervention* scenarios. If the factors that are excluded in the model do not have a different overall effect in the intervention scenario than in the reference scenario – such as an improvement in treatment of a disease, that lowers the disease specific mortality rate – these affect all scenarios and should not alter the ranking of interventions.

⁷A nice aphorism in this context is: There are no right or wrong predictions, but only good or bad ones (methodologically speaking).

2.5 Review of Selected Computer Simulations used for HIA

A leitmotif of the DYNAMO-HIA is to learn from already existing models instead of creating a completely novel approach. This should ensure the development of a workable model based on sound evidence and existing experience. Hence, in our design we are guided by both, the desiderata described in section 2.3 and an evaluation of existing software. Currently, no existing model does fully comply with all desiderata. Models that score very high on the technical requirements are normally designed for internal use and are tailored to the specific data situation of a certain country. Furthermore, they often require advanced programming skills and in-depth knowledge of the program. On the other hand, models which are specifically designed for public use are (virtually) exclusively intended for a single disease or risk factor, respectively, hence not being able to model overall population health.

In this section we give a brief account of the most important models reviewed for the purpose of DYNAMO-HIA. We outline their most attractive features for an HIA tool and the characteristics which makes them less suitable for a general, widely usable HIA tool. The selection criteria for the models that mainly guided our design process are outlined in section 7.3 where also detailed vignettes of these models are presented. Furthermore, we give in the appendix (section 7) an overview of all reviewed models (including search strategy).

Proportional Multi State Life Table (MSLT)

The proportional multi state life table [Barendregt et al. 1998] has a number of attractive features for HIA. First, it can model multiple diseases and assess the effect of risk factors through these diseases on population health measures such as total life expectancy and DALE. The main weakness its is lack of dynamic modeling capability and thus it cannot show the development of health outcomes over time. It is, however, a very transparent tool that uses data that are widely available. A future HIA-tool should certainly account for this attractive characteristic.

PREVENT

PREVENT is a dynamic model that models a real life population through time. It is generic as it can be applied to several diseases and risk factors. Risk factors can be both, categorical and continuous, and a risk factor can be associated with more than one disease and a diseases can be a risk factor for other diseases. It is based on a epidemiological multi state model of chronic disease, using an incidence-prevalence-mortality framework. PREVENT includes disease-specific and overall population health outcomes, such as life expectancy and DALE. The presentation of the output of PREVENT clearly contrasts the reference and intervention scenario over time. A limitation of the current PREVENT version is that it does not model explicit risk factor states, but is based on the epidemiological effect measure: 'population impact fraction' (PIF). In doing so it operates at the population level. This reduces

the data requirements but as a result mortality selection cannot be handled and differences in risk factor exposure between cohorts are not included by default. Furthermore, PREVENT is not publicly available.

A future HIA tool should share with PREVENT the dynamic modeling of a real life population, using an IPM framework, the ability to handle both categorical and continuous risk factors, and the possibility to have diseases that can be risk factors for other disease. Moreover, the graphic output possibilities of PREVENT allow a comfortable communication of the simulation results. The future DYNAMO-HIA tool should build on the PREVENT model by implementing many of PREVENT's output possibilities.

ARMADA

ARMADA is a dynamic software specially designed to fit within a health impact framework. Among its attractive features is a generic disease model that allows to model complex disease processes and co-morbidity explicitly. Diseases can be risk factor of other diseases, remission can be modeled, and chronic diseases – in principle – with an arbitrary large number of progression states. A future HIA should strive for a similar flexibility in its disease model. A limitation of ARMADA for a broader user base, however, is that it requires the explicit specification of transition rates between every disease- and risk-state combination. These data are rarely directly available but need to be calculated from epidemiological data. Methods to calculate the transition rates from epidemiological data are not available within ARMADA. Moreover, the simulated

length of the time step is equal to the age categories of the population, hence requiring more detailed data for a more detailed projection path. Furthermore, ARMADA is not (yet) publicly available.

RIVM-CDM

The RIVM-CDM contains many already mentioned features that are desirable for a future HIA-tool. It is a dynamic model, and thus provides information on the development of health outcomes over time. It provides not only disease-specific but also overall population health outcomes, such as life expectancy and DALE. Additionally it links risk factors to multiple diseases and death and is based on a multi state model of chronic disease, using an incidence-prevalence-mortality framework. A marked feature of the RIVM model is that it contains modules that translate data-input from epidemiologic sources into transition rates, and into initial values for the starting population by age, sex and risk factor and disease. However, the model is not publicly available, and moreover is implemented in the commercial software Mathematica, which is not easily accessible to many potential users of an HIA-tool. Also the model is tailored to fit to existing Dutch data, and hence is too specific to be used with data across Europe. A future HIA-tool should include modules for translating standard epidemiological data into transition rates between risk factor states. DYNAMO-HIA will include this feature based on the existing RIVM-CDM modules.

POHEM

POHEM is a discrete event simulation (DES) developed by Statistics Canada. It is a very comprehensive software which has been used in a wide array of applications, among them cost-effectiveness analysis and policy evaluation for several diseases. It has been tailored to the Canadian context where Statistics Canada has access to individual (and longitudinal) data on health and socio-economic status (income, marriage status etc.) and can simulate the behavior of a dynamic population (not only health but also, for example, labor market and marriage behavior). With those data very complex policy questions can be simulated, but access to such data is very limited within the European theater. Furthermore, a DES framework is very time-consuming to design and implement and only has added value with very detailed, matching data, moreover, it cannot account for continuous risk factors. POHEM itself is not publicly available.

Foresight Obesity Simulation

The Foresight Obesity Simulation (FOS) consists actually of two parts. The first is a regression model to estimate future prevalence of BMI. The second part is a micro simulation which quantifies the effect of a single risk factor (BMI) on the incidence, total life expectancy, and costs of several diseases. A distinctive feature of FOS is the ability to accommodate an external projection of risk factor prevalence (through a regression model) within the dynamic simulation. FOS uses an individual sampling model and is still under development and not publicly available.

Table 2.2: Applying criteria to selected models (and further model characteristics)

Model	publicly available	heterogeneous	dynamic or static	modeling of risk factors and epidemiologic data	generic	outcome measures	real population	model type	uncertainty
ARMADA	no	sex and age groups	dynamic	explicit risk states, needs externally provided transition rates	yes	increased (or decreased) mortality and morbidity by cause	yes	dynamic life table	no
Foresight Obesity 2	no	sex and age groups	dynamic	explicit risk factor states, risk factor prevalence calculated externally	partly (only as Risk Factor)	LE and disease costs	yes	Individual Sampling Model	no (for the simulation part)
POHEM	no	individual	dynamic	unlimited risk factor states, individual level data	yes	LE, DALE, costs	yes	Discrete Event Simulation	yes (in parameters)
PREVENT	no	sex and age groups	dynamic	Par/Pif, aggregate data	yes	LE, DALE, costs	yes	dynamic life table	no
MSLT	yes	sex and age groups	static	Par/Pif, aggregate data	yes	LE, DALE	no	period life table	no
RIVM-CDM	no	sex and age groups	dynamic	explicit risk factor states	yes	LE, DALE	yes	several (dynamic life table and ISM)	experimental option for RR

Section 3

Computer-Based Simulations

A computer simulation for the purpose of HIA tries to answer the question *What if?* by simulating a policy intervention using a model and yielding numbers that allow to assess the effects of an intervention on population health compared to a baseline scenario. In this section we start with giving a stylized overview of some terminology and concepts used in the field of computer simulation. We then describe five different modeling approaches that have been used for HIA tools in the past. The description focuses on the strengths and weaknesses of these approaches. There is usually a trade-off between realistic and detailed modeling on the one side versus high implementation costs, transparency and (almost) prohibitive data needs on the other. We then outline the different approaches of disease modeling within a multi state modeling framework. Moreover, we outline some considerations about how to include the policy effect in a simulation. Finally, we outline how to evaluate and validate

a (computer) simulation model.

3.1 Terminology of a Computer Simulation

Considerations about building computer simulations can be split in two parts. The functional elements of a computer simulation and the substantive side – how the theory about the disease process is modeled. This dichotomy is somewhat artificial, as certain substantive features require the use of certain functional elements and vice versa.¹

3.1.1 Functional Elements

In this subsection we review briefly the most important functional elements of a computer simulation. Those provide the framework in which the disease process is modeled and simulated. In Table 3.1 a stylized overview of functional elements of a computer simulation is given.

Time Reference The *time reference* of a computer simulation can be either *static* or *dynamic*. A static simulation model yields the change between two time points (current vs. steady state) whereas a dynamic simulation describes the development over time. Both might yield the same prediction about the

¹A good example is the modeling of interactions. A computer simulation that right from the beginning does not include interactions between entities cannot be used to model infectious diseases (e.g. interaction between susceptibles and already infected). However, a computer simulation that explicitly models interactions might be usable for chronic disease modeling by setting the interaction to zero. But again, please keep in mind that this is a heuristic dichotomy.

Table 3.1: Stylized Overview of the Functional Elements of Computer Simulations [Becker et al. 2005; Law and Kelton 2000; Brennan et al. 2006; Habbema et al. in press]

Functional Element	Dimension	
Time reference	Static	Dynamic
Time Model	Discrete	Continuous
Change of State	Deterministic	Stochastic
Entity Level	Individual	Aggregate

future, but only a simulation with a dynamic time frame can tell what different states were occupied in between. Hence, a dynamic model describes how the process evolves over time.

Time Model If the choice has been made to use a dynamic time reference, the question arises how time is simulated. The time model can be *discrete* or *continuous*². In discrete time the simulation is round based, every round encompasses a fixed time length, such as one year. In continuous time, time steps are not explicitly distinguished but a continues function is used to calculate the waiting time to the next event. This difference can be of importance for the way the (disease) process in question is modeled; whether one assumes the variables to change continuously over time or instantaneously at a given time point. A third option is a *semi-discrete* set up. The general time model is still discrete, but continuous time is used within the rounds to calculate when an event happens (within this round). This has the advantage, that for

²Loosely speaking it is *pseudo*-continuous time as a digital computer cannot simulate real continuous time.

competing risks – e.g. two or more events happen in one simulated round that influence each other or are mutually exclusive – it can be clearly identified which is occurring first [Willekens July 2007].

Furthermore, it is important to consider what data is available to feed the model. If only annual data is available, a model using daily increments in the simulation would usually not increase the explanatory power.

Entity Level and Interaction The choice of the entity level that is simulated is somewhat heuristic. For a disease process the choices are: the individual level, a set of individuals (a cohort), or all individuals (a population). It is important to note that within an entity that is modeled homogeneity is assumed. When the entity level is chosen to be the cohort of all, say, 45-year old men, then only statements about this group as a whole can be made. Nothing could be said what happens within this set of individuals. This assumption allows a simplification in the design and is often reasonable. To allow more detailed analysis, the cohort can be differentiated further by splitting it up into, say, smokers and non-smokers, obese and non-obese and so on. This increases the number of distinctive entities to be simulated tremendously and may counteract the main advantage, simplicity, of using a cohort or a population as the entity level.

A simulation that chooses the individual as the entity overcomes this problem right away. Every individual possesses some characteristics that are of interest (say, smoking status and BMI) and is sent individually through the

simulation. Those characteristics now determine the transition probabilities used in each simulation run. The outcome is a set of biographies driven by the individual characteristics. To get a population estimate the derived biographies are aggregated. This leads to *simulation variability* as the individuals to be simulated (or better their characteristics) are drawn from random distributions.³

Interaction, in the context of the functional dimensions of a simulation, means whether the entities of a simulation and their current state influence other entities within the simulation. A health related example would be the modeling of infectious diseases where the dynamics of an epidemic depends on the size and behavior of the infected part of the population. For the purpose of chronic disease this issue is negligible.⁴

Change of state The change of state (or the change of a simulated variable) in a simulation can be either *deterministic* or *stochastic*. In the former case, what happens to the entity simulated at a given time step is non-random. In a stochastic simulation the values, responsible for the value change of the variables (*transitions*), are drawn from (specified) random variables.⁵ This means that no two runs of the simulation are exactly the same. So, for a

³This is sometimes called *first order uncertainty* [Karnon 2001](compare 3.1.2 for details).

⁴Although it might be worthwhile to model across generations (e.g. differences in children from smoker household vs. non-smoker households).

⁵This is sometimes called *second order uncertainty* [Karnon 2001] or *parameter uncertainty* [Briggs 2000].

stochastic simulation several runs are necessary to calculate what the expected outcome is and how certain it is (compare 3.1.2 for details).

3.1.2 Variability, Heterogeneity, and Uncertainty in Decision Models

Three key terms in a health related simulation (or decision) model are:

- *variability* – differences between individuals that occur by chance,
- *heterogeneity* – differences between individuals that can be explained, and
- *uncertainty* – the probabilistic aspect of a simulation modeling exercise.

We are going to discuss those in turn and relate them to a (hopefully) intuitive analogy of a regression model. The exposition follows Briggs et al. [2006].

Variability Variability refers the phenomenon that – when modeling individuals – there will be always some variation. For example, a group of individuals has a mortality rate of .5 for a given time period. After the time period we would expect half of the individuals being dead. But the outcome at the individual level is binary, either dead or alive. In cohort based model we would use the proportion of .5 to model the mortality and could avoid variability. In a individual level based simulation, however, we would observe a variation around the true probability of .5. The variability can be made arbitrarily small, though, by increasing the number of individuals simulated.⁶

⁶Sometimes dubbed first order uncertainty.

Heterogeneity Heterogeneity differs from variability in the sense that variation in the simulation outcome could be explained, given the necessary knowledge. In the above example, the mortality rate could actually differ by sex (say, .4 for women and .6 for males). If a model would include this parameter (sex) this source of variation would be reduced. Heterogeneity is not a form of true uncertainty, as we know with certainty whether an individual is male or female. What we do not know is if the mortality rates differs conditional on certain parameters.

Uncertainty The term uncertainty in a health model usually refers to the uncertainty around input parameters (second order uncertainty). From the example above, this would be the value for mortality. We might have a point estimate (from a study) that says males have a mortality of .6, but there is uncertainty – in the form of a confidence interval – around it.

Another form of uncertainty is the so called *model uncertainty*, sometimes also dubbed *structural* uncertainty. This refers to the lack of full knowledge whether the mathematical structure of the simulation model is capturing the real life phenomenon truly. One has to note that the concept of model uncertainty derives from the field of statistics, where models are usually somewhat simpler and it is less onerous to test different specifications.

Regression Analogy Think of a standard linear regression model:

$$Y = \alpha + \sum_{i=1}^k \beta_i X_i + \epsilon$$

In this analogy the dependent variable Y would be the output of the simulation model. The coefficients α and β are the input parameters of the model. Now, the coefficient β models the *heterogeneity* in the sense that different values of X lead to different values for Y . To capture additional heterogeneity an additional characteristic (variable X_k) and input parameter (β_k) is needed. The *parameter uncertainty* in an simulation model is similar to the standard errors of the regression estimates for the coefficients α and β_i . The *variability* of a simulation model is represented by the error term *epsilon*. The *model uncertainty* refers to the question whether we can truly assume an additive regression model, or whether, say, a multiplicative specification would be more appropriate.

3.2 Common Modeling Approaches in HIA

The presented selection of common modeling approaches is derived from actual models used for HIA (see appendix). Every reviewed model can be categorized in (at least partly) one of the following five approaches.

Decision Trees

Decision Trees are very simple models originating in decision analysis. Usually, at a given node, two options are modeled and assigned a probability. This is repeated at every node until a desired set of outcome states is reached. The model is at the aggregate level; to get population numbers a cohort is assumed and 'sent' through the decision tree. The probabilities of outcome give the fraction of the cohort that will reach this state eventually, hence the model is deterministic. The model is static as only one future state can be observed. No interactions between units are modeled.

Period Life Table

A basic approach is a period life table (or single cohort model). A fixed number (usually 100,000) of people is exposed to transition probabilities. It can be just a single transition that is modeled (say, mortality) or several transitions like disability, disease, and mortality. This approach allows two different interpretations. The first is the *cohort* interpretation: A single cohort is followed throughout time. The second is the *stationary population* interpretation: the life table is interpreted as a population in a steady state [Veerman 2007]. For the purpose of effect analysis, the simulation is run twice: the first time with the transition probabilities of the reference situation and the second time with the transition probabilities reflecting the change in the exposure to risk factors due to the intervention. Either the exposure changes to a different level or not. The model cannot accommodate policy interventions which develop

their effects over time (say, every year 10% of smokers quit). In the cohort based interpretation only statements about one cohort can be made. In the population based approach statements can be made about the population as a whole, but – as the model is static – it cannot be assessed when and by which path the steady state is reached.

Dynamic Life Table

Dynamic life tables intend to overcome the limitation of a period life table by adding the time dimension. A whole population divided into appropriate classes (say, sex and 5-year-age intervals) is modeled. Transition probabilities are applied to respective groups and determine the composition of the life table in the next time period.⁷ To allow for consistency of the interpretation also births are modeled, so that truly a whole population is simulated.

This model allows for varying the risk factor exposure over time as the transition probabilities can be altered for every time point. It is dynamic and allows to infer net changes of population health and the path by which they are reached.

In principle, the number of classes in which a population can be split up is not limited (so not only by age and sex, but also by disease status, socio-economic status and so on), but for this approach increasing the number of states also increases computational burden substantially.

⁷Example: The group for 40 to 44 year old men at time point t which contains 10,000 individuals has a .9 probability of staying healthy, a .05 probability of dying, and a .05 probability of disease. At $t+1$ the group of 45 to 49 year old men consists of 9,000 healthy individuals, 500 dead, and 500 diseased.

Individual Sampling Models

Individual Sampling Models (ISM) are closely related to dynamic life tables. They use a very similar model structure, but instead of modeling cohorts the entity simulated is the individual by creating life histories. A great advantage of such models is that they allow for heterogeneous populations. Transition probabilities can be adjusted given some characteristic of the individual, by that altering the inflexibility of a model using cohorts. From a computational point of view, ISM can accommodate a higher number of states given the same resources. This flexibility, however comes with a price. The computation time is usually higher and the outcomes are stochastic as every transition is decided by drawing from a random variable.

Discrete Event Simulations

Discrete Event Simulations (DES) are also set at the individual level. For every individual, the waiting times until all theoretical possible events are calculated and the individual then experiences the event with the shortest waiting time. From this given event (that may or may not change the number and transition probabilities to future events) again waiting times are calculated. Hence, these simulations are event-driven, the change of state is stochastic and takes place in continuous time. Interactions between entities can be modeled. This kind of simulations allow very complex models. But there are onerous to build and to utilize their full power, extensive data is needed.

3.3 Multi State Modeling of Chronic Diseases

An HIA tool has to account for the following causal chain: 'determinants \rightarrow risk factor exposure \rightarrow health state \rightarrow mortality'. For this part several important elements can be learned from the epidemiological modeling of (non-communicable) diseases. First, using an IPM (incidence-prevalence-mortality) framework gives insights into the progression of a disease over time and the different kind of mortality risks one has to take into account. Second, modeling using a compartmental /discrete time approach. A (basic) IPM-model utilizes the (mathematical) connection between related disease variables. The example illustrates a single-disease model (see Figure 3.1): An individual or a cohort, respectively, can be in either of four different states: healthy, diseased, dead from the disease, or dead from all-other causes.

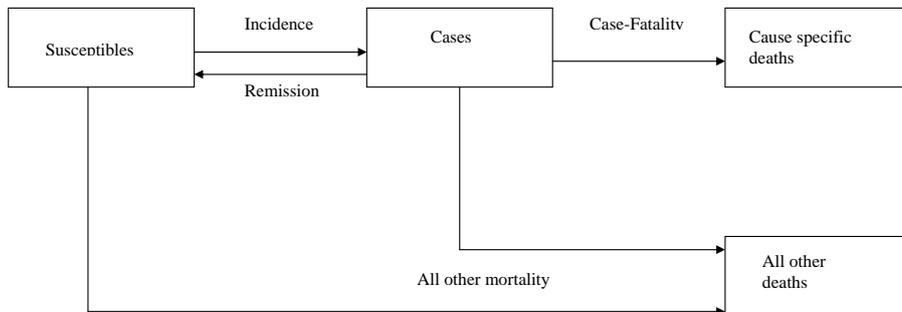


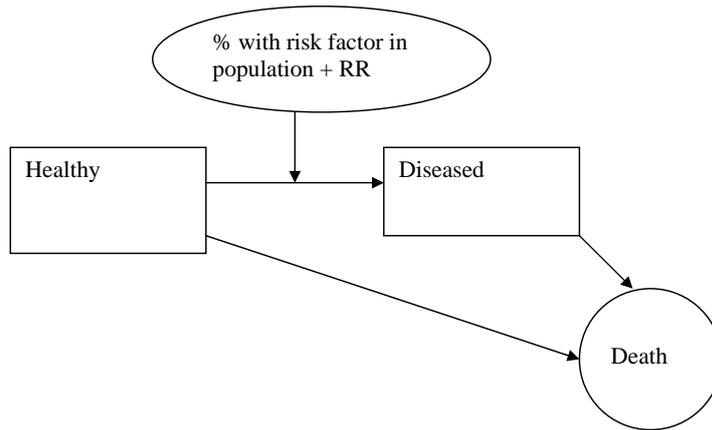
Figure 3.1: A conceptual markov model of a single disease within the IPM-framework. Source: [Kruijshaar et al. 2002]

However, such a set up might prove to be too simple. In particular the question how risk factors are incorporated into the model is crucial. Two common approaches can be identified: either explicitly creating states for risk factors (say, 'healthy and non-smoker' vs. 'healthy and smoker') or using the potential impact fraction (PIF) to alter transition rates (see Figure 3.2). The potential impact fraction $\frac{\sum_1^n P_i(RR_i-1)}{\sum_1^n P_i(RR_i-1)+1}$ – with RR and P being the relative risk at a given exposure level and the population level or distribution of exposure, respectively – quantifies the effect of the intervention on the transition rate (e.g. a PIF of .1 means that the transition rates after the intervention will be reduced by 10%). The main advantage of this model formulation is that no data on transition probabilities between risk factor states are needed. The relative risk and the prevalence of the risk factor are sufficient. However, this simplification of the disease model comes with a price: It does not account for *mortality selection* and ignores differences in *risk factor exposure for different cohorts*.

Mortality selection denotes the phenomenon that certain groups of individuals have a higher overall mortality risk and therefore are 'selected' out of a population over time. An example would be smokers and never-smokers: as smokers have a higher mortality risk, a higher proportion of smokers will have died after some years than in the other sub-populations. In the PIF approach, each subject, either smoker or never smoker is exposed to the same average risk and change in risk due to the intervention, ignoring the fact that smokers die out earlier than non-smokers. Hence, in a dynamic model – where the error

accumulates over time – and by that grows in size – a model without modeling risk-factor states explicitly will unavoidably produce a bias in the estimates.⁸

PIF-based model



Model with disease-risk factor states

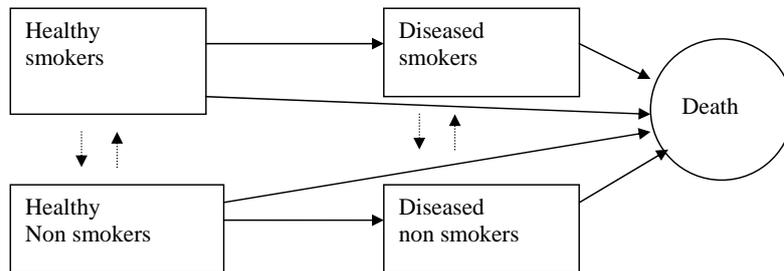


Figure 3.2: Comparison of PIF-based and Risk Factor models

The other limitation of the PIF approach for dynamic models is the limited possibility to include *cohort differences in past and future exposure*. In

⁸Little is known about the actual size of the bias and is certainly a function of the figures used [Bronnum-Hansen 1999].

a situation where successive birth cohorts have been exposed to unchanging transition rates between risk factor states (e.g. *constant* age and sex specific smoking start and quit rates), current prevalence of the risk factor (e.g. current, former and never smoking by age and sex) captures all relevant exposure information for disease models. However, for risk factors where transition rates have changed over time (e.g. due to environmental or behavioral change), (i) information on past exposure is additionally needed for risk factors with long-lasting effects, and (ii) future prevalence of the risk factor by age is not likely to be the same as the current exposure by age.

For risk factors (such as smoking), that have a lasting effect on disease risk (such as cancer where the effect of smoking is still present after quitting smoking), not only current risk factor exposure, but also past exposure influences the risks of disease onset and death. Past exposure can be taken into account - in a disease model that explicitly models risk factor exposure - by introducing extra risk factor states, which reflect past exposure (e.g. stopped smoking less than 1 year, stopped smoking 1-2 years, etc.). In a disease model without explicit modeling of risk factors - PIF-based models - the effects of past exposure can only be *partly* handled by including information on the prevalence of the risk factor (e.g. proportion of smokers) in the previous years. Partly, because risk factor prevalence in the entire past population is used, instead of in the current living population. There is a difference between the two as not the entire population in previous years is still alive and mortality differs by risk factors exposure (due to mortality selection relatively more smokers have died

than non-smokers).

When there are substantial differences between generations (birth cohorts) in past exposure, it is not realistic to assume that the current prevalence of the risk factor by age will be constant in the future. For instance, older generations of women (earlier birth cohorts) smoked less than younger generations today; and in the future - when the currently younger women will reach older ages - a larger proportion of them is likely to smoke than in today's older women. In a model with explicit risk factor states, this is automatically handled as predicting future risk factor exposure is part of the modeling of the risk factor. The future risk factor status is based on the current risk factor status (which reflects past exposure between birth and the current age) and (future) transitions between risk factors exposure categories.⁹ For models without explicit risk factors states, it is not straightforward how to deal with a situation where the current risk factor distribution by age is not likely to hold for more recent cohorts. It requires the future prevalence of risk factor (by age and sex) as input for the model. This would involve using a cohort model to generate the input, or such a model should be built in the PIF-based tool to generate these data.

Apart from how risk factors are included it is important whether *intermediate diseases* as a special kind of risk factors are included. Intermediate diseases are (chronic) diseases (e.g. diabetes) an individual can contract that change

⁹An exception is in a situation where the data on transitions are not available, and data on net transitions are estimated from the current prevalence assuming a steady state (e.g. constant transition rates between birth and current age). Then the future age distribution is the same as the current one.

the risk of getting another disease (e.g. CVD), hence acting as a risk factor. Ignoring this additional increase in risk for further diseases might substantially underestimate the health effects of a primary risk factor (such as BMI) and the effect of interventions targeting those primary risk factors.

The explicit modeling of risk factor states avoids the mentioned problems (see Figure 3.2 bottom). It can better account for differences in the exposure of risk factors over time and cohorts and different types of interventions (both, interventions affecting the initial risk factor distribution and interventions affecting transitions between risk factor states). Certainly, the PIF/PAR approach has merit due to its limited data needs, but when PIF/PAR are used to update prevalences in a dynamic model, bias may become substantive.

3.4 Embedding the Policy Effect

The effect of a policy on health is modeled via a change in risk factor exposure. Two options have to be considered: First, whether the behavioral response (and by that the change in risk factor exposure) to a policy is determined exogenously or endogenously and, second, whether the whole population is affected uniformly or if the effect depends (partly) on the characteristics of the entity modeled.

The first option, whether the individuals follow some decision rule given a policy change, is usually not part of an HIA tool. An example for an en-

SECTION 3. COMPUTER-BASED SIMULATIONS

Table 3.2: Choices for Embedding a Policy Effect

Size of Policy Effect is determined:	Uniform Effect on Entities	Differentiated Effect on Entities
Behavioral response to policy is exogenously	user determines change of risk exposure by a common factor for all entities	user determines change of risk factor for some entities
Behavioral response to policy is endogenously	n/a	entities react to a policy change given a pre-specified decision rule and depending on their characteristics

ogenous response would be a price change in, say, cigarettes. The change in risk factor exposure would then be conditional on the behavioral change of the respective individual. Whether he or she chooses to change his or her smoking behavior and by what magnitude depends on further personal characteristics: a rich long term smoker reacts certainly different to the same price increase than an occasional smoker who has no income. This, in principle, could be modeled, as it is done in the field of (micro) economics. Economists try to answer questions such as how many people pick up work if income tax is lowered; not everybody reacts equally to that. A wealthy person certainly reacts differently to a tax incentive than a poor person and so on.

But for modeling such decisions, one has to be aware that those are very complex models that need rich data to be able to construct the actual decision rule. The standard approach in HIA is instead to determine the size of the change of the risk factor exposure externally by, for example, using estimates

derived from econometric studies or expert opinions. This would mean that the risk factor exposure is changed directly by some fixed amount, say, 10% increased smokers cessation rate or 10% lower prevalence of smokers.

The second option, whether all entities are affected uniformly or not, has important ramifications on the complexity of the policies that can be modeled. An example for a uniform decrease in risk factor exposure is the reduction of overall pollution in the air as everybody can be assumed to be equally affected by that. Allowing to change risk factor exposure differentiated by some characteristics of the individual would translate into changes like: *The policy is targeted at female teenagers, hence 20% less 16 year old females start smoking whereas the reduction in 16 year old boys is only 5%.*

Further thoughts are concerning the timing of the effect. It is certainly more realistic that the change in risk factor exposure through a policy does not materialize at once, but takes some time do so, such as, say, an annual increase of tobacco prices. This would allow for changes like: *Every year 5% of all current smokers quit.*

3.5 Evaluation of HIA Simulations: Validity and Uncertainty

Validity To evaluate the validity of mathematical/computational models in the field of (medical) simulations is both an important and difficult task. Important, as – most likely – the model will be used to generate knowledge on

which decisions will be based. Difficult as a mathematical model – by its very definition – is always a simplification of a real life phenomenon. The question arises when the simplifications serve their purpose of finding a good enough solution for the task at hand or when the simplifications make the model just simplistic. A consensus has not been found to answer this question. However, several authors developed guidelines for the assessment of such models. For example, Buxton et al. [1997] give 5 recommendations for modelers. Sculpher et al. [2000] outline over 30 questions for appraisal of a used model. Weinstein et al. [2003] formulated guidelines for good practice in model building that list over 40 items (with several sub-items). In a synthesis of the literature Philips et al. [2006] develop a questionnaire consisting of more than 60 questions for the appraisal of a model. Despite the ever growing list of (overlapping) recommendations all share two central arguments: modeling is useful and full validity cannot be established.

These guidelines, however, consistently address three different areas of a model building exercise: structure, data, and validity or consistency. The overarching theme is transparency, the model designer should be able to explain in what ways the made assumptions alter the outcome.

Concerning the validity of a model the ISPOR task force differentiates between *face*, *internal*, *cross*, and *predictive* validity [Weinstein et al. 2003].¹⁰ The face validity asks whether the results are explainable at the intuitive level. The internal validity refers whether the implemented software is consistent

¹⁰This is a very similar notion to the three forms of validity as defined in section 2.4, with internal and cross-validity being elements of overall formal validity

with the specified mathematical model. Cross validity rests on the comparison of the simulation results to the results of other models, discrepancies should be explainable due to the model structure. Finally, predictive validity – although desirable – is not considered essential.

Parameter Uncertainty An open, but important question is to what extent a model should be probabilistic. The explicit incorporation of parameter uncertainty allows to quantify the uncertainty around the outcomes values of the simulation. The methodology used here is a *probabilistic sensitivity analysis* (PSA): given the distributional assumption made about an input parameter, random values for this parameter are drawn and the simulation is run many times with the drawn values. The different simulation results (one for each random draw) then give a distribution of the outcome in question (e.g. life expectancy) with a point estimate and a variation around it.

Although some consider a PSA the gold standard in decision modeling, it is not unanimously recommended [Weinstein et al. 2003; Halpern et al. 1998] due to several reasons. Conceptually, the choice of a distribution around the input parameters is non-trivial and not clear-cut. Furthermore, often (inappropriately) independence between the parameter distributions is assumed. Technically, a PSA could account for the correlation between parameters, but often the knowledge is lacking to properly specify such bi- or multivariate distributions. Pragmatically, the implementation of a PSA into a model is a costly and complicated task. Furthermore, the calculation time for the run of

a model increases tremendously and the model output increases in complexity, making an interpretation more difficult.

Model Uncertainty Despite its theoretical value, very little advice exists concerning the quantification of model uncertainty. A suggestion and practical application of model uncertainty for the case of standard life table has been done by [Tainio et al. 2007]. In addition to modeling parameter uncertainty they introduce model uncertainty via binary parameters. For certain assumptions about the model structure they develop binary alternatives (e.g. whether pollution has a causal link to cancer or not) and assign a probability for each option (e.g. a probability of .9 for "Yes" and .1 for "No"). Now they include values for this (structural) parameter in their PSA like an ordinary input parameter. In effect they constructed two different models and assigned a (subjective) probability which model is more likely. In the case of a (more complex) simulation this approach would require to design and implement a whole range of (very) different models.

Section 4

DYNAMO-HIA

4.1 Proposed Model Specification

We propose a *dynamic simulation tool* with *explicit* risk factor states (including *intermediate diseases*) for *annual, population-based* data that models *multiple* and *varying* chronic disease processes with a *discrete* time frame using a *multi state model (MSM)*. The model will be able to translate the epidemiologic evidence into individual *transition rates*. The user determines the effects of policies on risk factor exposure *exogenously* to the model. Several established *outcome measures* highlighting the effect of the interventions compared with the reference scenario will be readily calculated. It will be *publicly available*, accompanied with data for selected diseases and risk factors, an extensive *manual* including *illustrative applications* and recommendations for *policy scenario* building.

The tool should be *dynamic*, hence, being able to make predictions for single future time points and, furthermore, to show the effects of a policy on population health during the simulated time span (about 10 to 15 years are recommended, but longer time periods can be projected). A static model cannot specify the time needed to reach the simulated outcome and outcomes at intermediate time steps. Such insights, however, are important to better understand long and short term effects of a policy. The most commonly available epidemiologic data is collected *annually* and *aggregated* at the population level. This calls for a model in *discrete time* that can handle aggregated data. To be able to model the distribution of health gains and losses within a population, the tool should be able to model a sufficiently heterogeneous population. This can be done using elements of *micro simulation* (more precisely an individual sampling model (ISM)) as it has individuals as the entity while using a macro-level multi state model for the disease process.¹ By that established epidemiologic modeling standards can be used. Such an approach does not automatically increase the data needs compared to a cohort based approach. If fed with the same (aggregated) data as a cohort based model the same predictions will be achieved. But if more detailed data is available, the ISM approach is able to make use of it. The data needed to feed the model will

¹This approach is somewhat related to the UKPDS model. It uses a micro simulation to create "biographies" of risk factor history as those can be rather complex to model using cohort based models, in particular when the tool has to be generic to allow for different kind of risk factors. At the disease – where we specify three template disease processes – level the probabilities for incidence and mortality are then used deterministically to avoid undue random noise from individual sampling. The rationale behind this split is that some diseases have such low probabilities of incidence that large numbers of individuals would have to be simulated. We tentatively call this approach *partial micro-simulation*.

be of such a nature that it should be obtainable for (almost) all European countries.

The choice of modeling *explicit risk factors* avoids bias due to mortality selection and handles differences in risk factor exposure between cohorts. The use of a MSM approach is flexible enough to model various chronic disease processes, by striking the balance between sufficiently realistic disease modeling and technical feasibility. As modeling should be consistent with the epidemiologic data available, the tool will model the time dependency of exposures by linking relative risks to duration of being in a certain risk factor class (lag time). In the examples for which the model will be used, this will be illustrated with the effect of stopping smoking.

To avoid an overly complex model and assure that it is generic the change of risk factor exposure due to a policy should be determined *exogenously* by the user. The user should specify the intervention by either changing the prevalence in risk factor exposure or change the transition between risk factor states. Furthermore, the user should be able to differentiate the magnitude of the change according to certain population characteristics such as age, sex, or risk-factor status. This can be done with an ISM approach. Furthermore, the ISM approach is – in principle – open to model decision making within the simulation, allowing for the necessary flexibility for further developments of the tool. The population projections will be done using birth figures from external sources (e.g. EUROSTAT or from the respective national statistical offices). Migrants and migration will not be modeled. For the former – migrants –

very rarely risk factor or disease specific data is available to justify the added complexity. The latter – migration – is very difficult to model² and its inclusion would not alter the overall outcome of the modeling exercise assuming that the decision to migrate is independent of health determinants. Furthermore, changes in future (overall) mortality are not modeled (apart from changes caused by changes in risk factor exposure).

The presented output serves two purposes: i) communicate the *differences* between the reference scenario and the intervention scenario and ii) to increase *transparency* to let the end user check and understand the intermediate steps how the presented output was derived. Since the model specification of the model has multi state modeling as its core a whole range of *outcome measures* can be presented such as disease incidence, and disease prevalence. In addition, overall health measures, such as life expectancy, life years lost, or number of deaths prevented can be obtained from the tool. Outcomes generally can be differentiated by age, gender and calendar year. The choice of outcome measures that will be provided to the user has to be conducted carefully, taking into account the wishes of HIA experts and known caveats of the measures as some measures might be misleading.

The tool will be *publicly available* to encourage a broad user base and increase the verifiability the scientific community. User friendliness of the program is a priority concern. This, of course, requires to design a user interface that does not expect more than basic computer literacy. The graphical user

²As some put it: One cannot model migration for a given country without modeling the rest of the world as well.

interface should strive to be intuitive and self-explanatory. Furthermore, the simulated output should be easily exportable to other programs used for the presentation of the results. No specialized software should be required; the tool should either come as stand-alone, platform independent software. The tool will be accompanied by an extensive *manual* that also includes illustrative examples with the accompanied data. It will give advice on how to construct scenarios to compare different policy interventions and to conduct a sensitivity analysis (see below).

The user targeted is more likely a practitioner than a research scientist. To strike a balance between a sufficiently realistic model and applicability by limiting data needs, we decided to simulate a *single* risk factor (three kinds are possible: categorical, continuous, and duration of class membership; for more details see section 5). In the case of a categorical risk factor up to nine different risk factor categories can be specified. Although the number might seem low at first, nine categories still allow for a sufficient degree of complexity as risk factors combinations are possible such as "‘smoker with high socioeconomic status’", "‘smoker with low socioeconomic status’", "‘non-smoker with high socioeconomic status’" and so on. One should keep in mind that for such models the problem is not so much to increase the number of risk factor classes, but to get the necessary empirical data to feed such a model. Hence, we believe that the chosen number of risk factor classes is a good compromise between complexity and ease of use.

4.2 Achieving Validity

To achieve overall validity for the proposed model, we follow a strategy we loosely label *evidence synthesis* by focusing on the two elements (model structure and data) which are under our control right at the beginning of the model building exercise. The disease model being proposed and implemented is well founded in epidemiological evidence (such as using multistate modeling of chronic disease with explicit risk factor states and inclusion of intermediate diseases). Furthermore, the design of the model was undertaken in close cooperation with experts in the field, that assessed the availability of certain disease (cancer, CVD, and COPD) and risk-factor (smoking and BMI) data. Hence, the model structure was designed in such a way that it does not depend on data which is difficult or very costly to obtain, but can be used with data which is available for most EU-countries. A crucial issue with disease data (incidence, prevalence, mortality) is whether they are internally consistent as consistency is a necessary pre-condition for a modeling exercise. In particular for a dynamic model as the size of the error increases with each time step (*propagation of error*). Validity of disease data can be checked and achieved by the use of publicly available software.³

The careful designing and implementation of the tool with appropriate *quality data* should ensure *face* and *formal* validity (consisting of *internal* and *cross* validity) of the model. Internal validity, of course, will be established

³A well known tool – developed within the Global Burden of Disease project – for achieving internal consistency is *DisMod II* which can be downloaded at the WHO homepage (<http://www.who.int/healthinfo/boddismod/en/index.html>).

by careful testing of the software itself during the implementation phase. We intend to assess *cross validity* by comparing the DYNAMO-HIA model with already existing models in the field (such as PREVENT, MSLT, or RIVM-CDM) using a facile, well-understood benchmark intervention-scenario.

Concerning the *predictive* validity of the tool certainly no genuine promises can be made, except using an accepted and coherent model structure in conjunction with accepted quality data. Furthermore, one should bear in mind that an HIA tool always compares a reference scenario with an intervention scenario that are both projected by the same model. An excluded factor – such as an improvement in treatment – that affects both scenarios equally and hence does not alter the ranking of interventions.

The robustness of the results can be assessed by conducting a one or multi-way sensitivity analysis. In the former case, one input parameter is varied to extreme (minimal and maximal), yet plausible, values to gauge its effect on the overall model outcome. In the case of a multi-way sensitivity analysis several input parameters are varied at once. To keep the number of simulations to be run – and the forthcoming output – at a manageable level, the suggested protocol is to develop a limited number of scenarios (e.g. worst case, best case, medium case) and to report their outcomes. We will not, at this stage, include a probabilistic sensitivity analysis (PSA) in the tool. This has mainly pragmatic reasons. It is costly and time intensive to implement and cannot be easily done within the given resources. We estimate that it would double the programming efforts within our project. One has to note, however, that

the chosen model structure does allow for the implementation of a PSA in the tool at a later time point, given the necessary resources. Furthermore, a PSA is in its conceptual interpretation not straightforward. It requires a lot of additional data – or at least informed assumptions – about the shape of the random distribution to be chosen for the random draws. Additionally, a truly meaningful PSA should allow for the correlation of the random variables, increasing the need of data even further. Without a PSA, however, the model still yields the *expected outcome*, just the variation around the outcome cannot be assessed. In particular considering the nature of HIA-applications, in which changes in exposure are compared, this is often sufficient.

Section 5

Technical Outline of DYNMAO-HIA

The proposed model is in the form of an individual sampling model (ISM) combining elements of micro simulations with a multi state model. This means that first a population of individuals is generated, based on the data that are given to the model, like percentage of smokers, percentage of persons with diabetes etc. Secondly, the lives of these individuals are simulated over time (simulation module), both in the current situation (which we will further call the reference scenario), and under one or more policy scenarios. The model will be able to construct scenarios reflecting either of the following two types:

- risk factor prevalence in initial population is changed (for example the percentage smokers can be reduced in the baseline year to reflect a policy that reduces smoking in the population)

- transitions between risk factor states are changed (for example the quit rates of smoking can be increased to reflect a policy that increases quitting of smoking)

From the simulated life courses, the difference in population health outcomes between the reference scenario and the policy scenario(s) will be calculated. Proposed outcomes are at least:

- Differences in the number of persons with a specific disease by age, sex, and calendar year
- Differences in total mortality number and rates by age, sex, and calendar year
- Differences in the number of life years lived
- Differences in the number of disability/health adjusted life years lived

Also the model will generate an output file containing detailed data for all simulated years, so that researchers can make their own summary measures, or can use the data in economic evaluations etc.

Figure 5.1 shows the general model proposed. The input of the model consists of data on the population level. In order to be used in the simulation, averages for the overall population have to be translated first in parameters for transition rates on the individual level. For instance, the input incidence rates reflect average incidence rates in the population. On the individual level, for example one needs a different incidence rate for a smoker and a non-smoker. In general, the individual rate will be parameterized by assuming that the

individual incidence rate is equal to a baseline incidence rate times relative risk. The latter will depend on the risk factors of the individual. The goal of the parameter estimation module of the program is to estimate the parameters needed to simulate individual transition rates. In the example, the parameters needed are the baseline incidence rates and the relative risks. The latter are direct input to the program, but the first needs to be estimated from the population incidence rates, risk factor prevalence, and relative risks. Also, the input data are not sufficient for the generation of an initial population. For instance, while the input data will provide information on how many smokers there are, and how many persons with a stroke, they do not provide direct information on the number of smokers with a stroke. In the proposed model these numbers will be estimated using amongst the relative risk of smoking on stroke, the proportion of smokers, and population prevalence of stroke (an overview about the parameter estimation module is given in table 5.1).

Model input In the following section we will list the input needed by the model. Unless otherwise specified, all input is needed in 1 year age classes and by gender. The input should have been checked for inconsistencies: specifically the disease data (incidence, prevalence, and excess mortality) should be generated using, for example, the DISMOD program, and be smoothed. Also the risk factor data are assumed to be smoothed.

The following input from data is needed:

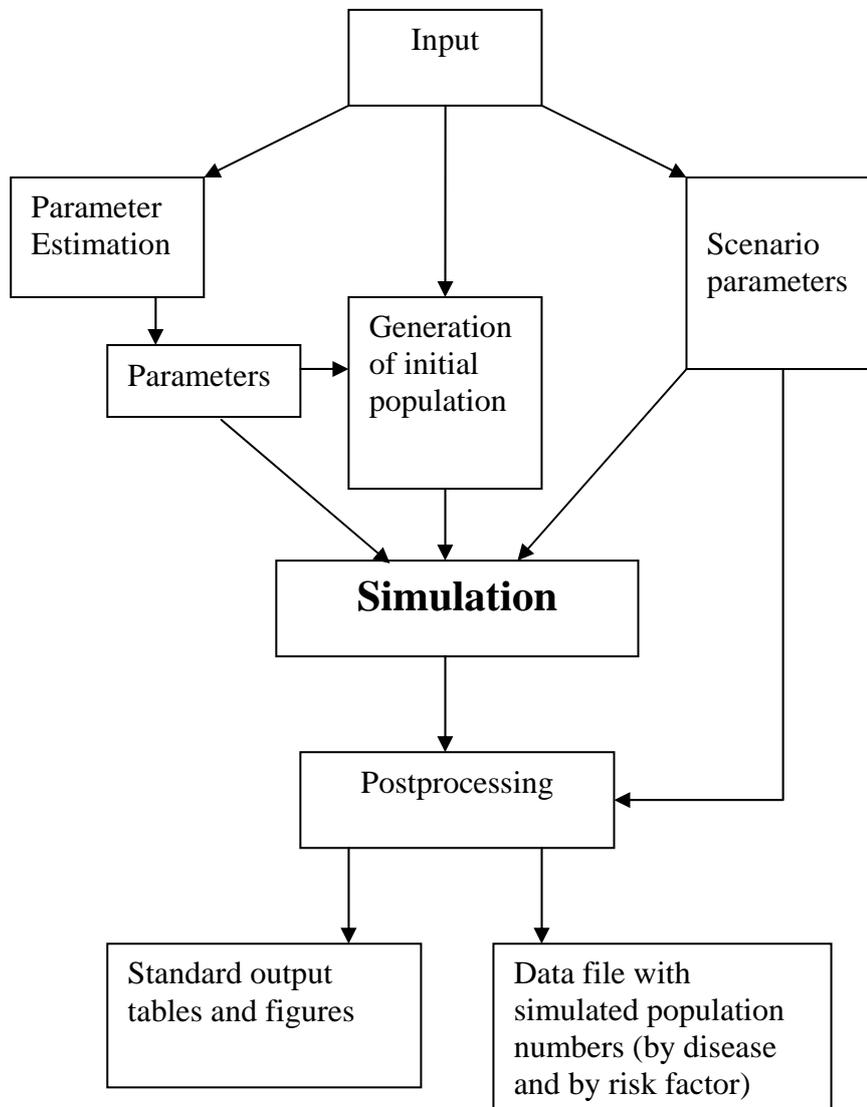


Figure 5.1: Conceptual framework of proposed simulation.

- Population numbers
- Total mortality rates
- Number of births in future years
- Prevalence of risk factors – those can be in one of three forms:
 - A risk factor with a continuous distribution (for instance BMI); in this case the input needed is: the shape of the distribution (normal or lognormal), mean of the distribution and the standard deviation.
 - A risk factor in classes (for instance: smokers / former smokers / never smokers): the percentage in each class. A maximum of 9 classes can be entered in the program.¹
 - A risk factor in classes (as above), but with the addition that for one class also the duration of being in this class is of interest (for instance in case of smoking the duration of having stopped smoking is of interest). Here we need as input (besides the percentage in each class) also the distribution of the duration of stopping. This distribution will be asked for in a parametric fashion (asking for the shape of the distribution and for instance average stopping duration) or in a non-parametric fashion (asking for the percentage of stoppers that has stopped 1 years, 2 years, 3 years etc.). Alternatively, the initial distribution can be uniformly distributed.

¹The implementation of 9 categorical risk factor classes implies that already 16200 transitions must be specified: From each risk factor category to another risk factor category for each age group by sex ($9 \times 9 \times 2 \times 100 = 18200$).

Only one risk factor can be entered in the model. However, the user could use the 9 classes available to define "compound risk factors" like "smoking alcohol drinkers".

- Incidence rates of the diseases: Note that the definition of incidence rate here is the number of new cases per person-year in those without the disease.
- Acute fatality of disease: For diseases that are acutely fatal for a part of the population, while leading to a chronic condition in others (like stroke or myocardial infarction), the percentage of events (both first time and recurrent events) that is acutely fatal. The precise definition of "acute" (for instance within 1 day, within 30 years or within 6 months) is left to the user. This definition should be chosen in such a way that the mortality rate after the acute period should be approximately constant (apart from a possible increase due to aging).
- Excess mortality /Case fatality rate of the disease: this is defined as the difference in mortality rate between those with the disease and those without the disease (adjusted for age and gender)

OR

- Relative survival of the disease: this is defined as the ratio of the mortality in those with the disease versus the mortality in the general population (adjusted for age and gender). This can be given as a constant

rate over time or at different points in time after diagnosis (by age and sex).

- Prevalence rate of the disease
- Relative risk of the risk factor on the disease. For a continuous risk factor the relative risk for one unit increase in the risk factor should be given. For a risk factor in classes relative risks should be given for each class separately. In case a duration variable is added to the classified risk factor, a relative risk at duration=0 (for decreasing risk with time) or at duration=10 (for increasing risks) should be given, as well as the duration at which the excess risk is halved. (That is: $(RR-1)$ is 50% of $(RR-1)$ at duration=0 or 10).
- Relative Risk of total mortality
- Relative Risk of contracting a disease given an intermediate disease (if included)
- Transition probabilities between risk factor categories² (optional)
- DALY weights for the general population
- DALY weights for each disease

²This can be calculated by DYNAMO-HIA from the prevalence of the risk factor assuming steady state and one direction of transition

Diseases We distinguish the following type of diseases:

Independent diseases: With independent we mean that the risk of these diseases does not depend on the presence or absence of other risk factors. *Dependent diseases:* These diseases can depend on the presence/absence of an independent disease, but not on the presence/absence of another dependent disease. *Intermediate diseases:* These are independent diseases that are themselves a risk factor for a dependent disease – such a disease has an intermediate role in the causal pathway between risk factors and the dependent disease.

The basic model will include disease processes describing all chronic diseases for which the excess mortality (defined as the difference in mortality rate between those with the disease and those without the disease) only depends on age and gender, but not on how long one has the disease. This type of disease process is also included in DISMOD II [Barendregt et al. 2003a] software to estimate consistent incidence, prevalence and mortality rates deals with this type of disease process.

However, the assumption, that the excess mortality does not depend on the duration of the disease is violated for two types of diseases included in DYNAMO-HIA. First, for diseases like myocardial infarction or stroke, with a very high mortality rate immediately after the event, followed by a period with a constant but higher risk than in the general population. And, second, for diseases like cancer, where the excess mortality depends on duration of the disease through an exponential or Weibull function. The latter type of disease process is included in MIAMOD software. In order to keep the model simple

and to model all diseases in a similar fashion, we propose only to implement the exponential function, which implies a constant mortality rate. However, we will implement the often used mixture-cure model in order to accommodate non-fatal cancers. In sum, up to three types of disease processes could be accommodated by the model:

- A *chronic disease*, for which the excess mortality (defined as the difference in mortality rate between those with the disease and those without the disease) only depends on age and gender, but not on how long one has the disease.
- A *partly acutely fatal disease*: This are diseases (like myocardial infarction or stroke) that occur as a distinct event, that has a very high mortality rate immediately after the event, while those who survive this critical period have a higher mortality than the general population. However, after the critical period the excess mortality rate, like in the first disease process, depends only on age and gender, and not on the duration of the disease.
- A disease in which the excess mortality is *constant* in one group, while the excess mortality is zero in others (cured fraction). As the part of the patients that are 'cured' can only be identified in retrospect (after all diseased that have not been cured have died), it is less realistic to model 'cured' with remission [Yu et al. 2004].

Table 5.1: Overview of parameter calculations for the subgroups from population level input data: An example for a population with two risk factor groups (*smokers vs. non-smokers*) and two independent diseases (*diabetes and stroke*) and no acute fatal mortality.

Input at the population level <i>(Examples are in italics)</i>	Subgroup parameters derived at a prior step	Assumptions	Result: Parameter at subgroup level <i>(Examples are in italics)</i>
PREVALENCE OF DISEASES			
Prevalence of risk factor - <i>Prevalence of non-smokers</i> - <i>Prevalence of smokers</i>		Risk factor prevalence odds ratio equals incidence RR	Disease prevalence by subgroup - <i>Prevalence of diabetes in non-smokers</i> - <i>Prevalence of diabetes in smokers</i> - <i>Prevalence of stroke in non-smokers</i> - <i>Prevalence of stroke in smokers</i>
Disease prevalence - <i>Prevalence of diabetes</i> - <i>Prevalence of stroke</i>			
RR risk factor on disease onset - <i>RR smoking on onset of diabetes</i> - <i>RR smoking on onset of stroke</i>			
INCIDENCE OF DISEASES			
Disease incidence - <i>Incidence of stroke</i> - <i>Incidence of diabetes</i>	Disease prevalence by subgroup	Risk factor prevalence over age, does not change in time	Disease incidence by subgroup - <i>Incidence of diabetes in non-smokers</i> - <i>Incidence of stroke in non-smokers</i> - <i>Incidence of diabetes in smokers</i>
Prevalence of risk factor - <i>Prevalence of non-smokers</i> - <i>Prevalence of smokers</i>		Conditional on the risk factor, the disease incidence rates are independent	
RR of risk factor on disease onset - <i>RR smoking on onset of diabetes</i> - <i>RR smoking on onset of stroke</i>			
TOTAL MORTALITY			
Total mortality - <i>Mortality rates of the total population</i>		Risk factor prevalence over age, does not change in time	Total mortality by subgroup - <i>Total mortality in non-smokers</i> - <i>Total mortality in smokers</i>
RR of risk factor on total mortality - <i>RR smoking on total mortality</i>			
Prevalence of risk factor - <i>Prevalence of smokers</i> - <i>Prevalence of non-smokers</i>			

Table 5.2: Overview of parameter calculations for the subgroups from population level input data: An example for a population with two risk factor groups (*smokers vs. non-smokers*) and two independent diseases (*diabetes and stroke*) and no acute fatal mortality (continued).

Input at the population level <i>(Examples are in italics)</i>	Subgroup parameters derived at a prior step	Assumptions	Result: Parameter at subgroup level <i>(Examples are in italics)</i>
MORTALITY ATTRIBUTED TO DISEASES (CONSTANT SURVIVAL)			
Excess mortality of each disease - <i>EM for diabetes</i> - <i>EM for stroke</i>	Disease prevalence of each disease by subgroup	Attributable mortality does not depend on duration or risk factor	Mortality attributable for each specified disease - <i>Mortality attributable to stroke</i> - <i>Mortality attributable to diabetes</i>
Prevalence of risk factor - <i>Prevalence of non smokers</i> - <i>Prevalence of smokers</i>	Total mortality by subgroup	Attributable mortality is corrected for double counting	
OTHER CAUSE MORTALITY (OM)			
Prevalence of risk factor - <i>Prevalence of non-smoking</i> - <i>Prevalence of smoking</i>	Total mortality by subgroup Disease prevalence by subgroup	Other cause mortality does depend on age, sex and risk factor exposure	Other cause mortality by subgroup - <i>Other-cause mortality in non-smokers</i> - <i>Other-cause mortality in smokers</i>
	Attributable mortality to each specific disease (not by subgroup)		

Section 6

Appendix A: Overview of Collaborating Partners and Consulted Experts

The authors wish to thank all those who have provided suggestions to the model specification during the design phase (at the Dynamo-HIA workshop on 23rd of May, 2008, and by personal communication). They graciously supported us with their knowledge and expertise in designing the proposed model. The final responsibility with the model specification, however, rests solely with the authors of this document

SECTION 6. APPENDIX A: OVERVIEW OF COLLABORATING
PARTNERS AND CONSULTED EXPERTS

Table 6.1: Overview of collaborating Partners and consulted Experts

Name	Institute	Country
Albreht, Tit	Institute of Public Health of the Republic of Slovenia	Slovenia
Aradottir, Anna Bjoerg	Directorate of Health, Reykjavik	Iceland
Baili, Paolo	Instituto Nazionale dei Tumori (INT)	Italy
Barendregt, Jan J	School of Population Health, University of Queensland	Australia
Benett, Kathleen	Trinity Centre for Health Sciences, St James Hospital / Haughton Institute	Ireland
Branca, Francesco	WHO Regional Office for Europe, Copenhagen	Denmark
Brønnum-Hansen, Henrik	National Institute of Public Health, University of Southern Denmark	Denmark
Capewell, Simon	Professor of Clinical Epidemiology, Division of Public Health, University of Liverpool	United Kingdom
Critchley, Julia	Institute of Health and Society	United Kingdom
Dargent, Guy	European Commission, Public Health Executive Agency	Luxembourg
De Vries, Esther	Department of Public Health, ErasmusMC	The Netherlands
Den Broeder, Lea	National Institute of Public Health and the Environment (RIVM)	The Netherlands
Erkki, Vartiainen	Department of Epidemiology, KTL	Finland
Escoval, Ana	School of Public Health, Lisbon	Portugal
Fehr, Rainer	Institute of Public Health, North Rhine-Westphalia	Germany
Fernandez, Esteve	Institut Català d'Oncologia / IDIBELL	Spain
Fischer, Krista	Department of Public Health, University of Tartu	Estonia

SECTION 6. APPENDIX A: OVERVIEW OF COLLABORATING
PARTNERS AND CONSULTED EXPERTS

Name	Institute	Country
Galan, Adriana	Institute of Public Health, Bucharest	Romania
Hooijdonk, Carolien	Department of Public Health, ErasmusMC	The Netherlands
Janik-Koncewicz, Kinga	Marie Sklodowska-Curie Memorial Cancer Centre	Poland
Kalediene, Ramune	Faculty of Public Health, Kaunas University of Medicine	Lithuania
Kunst, Anton	Department of Public Health, ErasmusMC	The Netherlands
Lang, Katrin	Department of Public Health, University of Tartu	Estonia
Lauer, Jeremy	World Health Organization	Switzerland
Lobstein, Tim	International Association for the Study of Obesity	United Kingdom
Mackenbach, Johan	Department of Public Health, ErasmusMC	The Netherlands
Mathers, Colin	WHO Headquarters	Switzerland
McCarthy, Mark	University College London	United Kingdom
McKee, Martin	London School of Hygiene and Tropical Medicine (LSHTM)	United Kingdom
Micheli, Andrea	Instituto Nazionale dei Tu- mori (INT)	Italy
Norheim, Ole Frithjof	Department of Public Health, University of Bergen	Norway
Parry, Jayne	Public Health, Epidemiol- ogy and Biostatistics, Uni- versity Birmingham	United Kingdom
Philalithis, Anastas	Health Planning, University of Crete	Greece
Pomerleau, Joceline	London School of Hygiene and Tropical Medicine (LSHTM)	United Kingdom
Rabl, Ari	Consultant on environmen- tal impacts	France
Rehm, Juergen	Centre for Addiction and Mental Health, Toronto	Canada
Rutter, Harry	National Obesity Observa- tory	United Kingdom

SECTION 6. APPENDIX A: OVERVIEW OF COLLABORATING
PARTNERS AND CONSULTED EXPERTS

Name	Institute	Country
Sakallarides, Constantino	Escola Nacionale de Salud Publica, Lisbon	Portugal
Schaap, Maartje	Department of Public Health, ErasmusMC	The Netherlands
Smit, Jet	National Institute of Public Health and the Environment (RIVM)	The Netherlands
Soerjomataram, Isabelle	Department of Public Health, ErasmusMC	The Netherlands
Ünal, Belgin	Department of Public Health, University School of Medicine Izmir	Turkey
Ungurean, Carmen	Department of Strategy and forecast in Public Health, Institute of Public Health Bucharest	Romania
Van der Heyden, Johan	Scientific Institute of Public Health	Belgium
Vartiainen, Erkki	National Public Health Institute	Finland
Veerman, Lennert	School of Population Health, University of Queensland	Australia
Villerusa, Anita	Department of Public Health, Riga Stradins University	Latvia
Vitrai, Jozsef	HealthMonitor, Nonprofit Public Purpose Ltd.	Hungary
Walls, Helen	Department of Epidemiology and Preventive Medicine Faculty of Medicine, Nursing and Health Sciences, Monash University	Australia
Wolfson, Michael	Statistics Canada	Canada

Section 7

Appendix B: Review of Existing Models

7.1 Search Strategy

Several different search strategies were used to identify software tools for quantitative effect analysis within an HIA framework. First, and foremost we used a survey of experts in the field of HIA and simulation modeling. This survey was augmented with an informal inquiry on the email lists 'Health Impact Assessment for the United Kingdom and Ireland' and 'Asia Pacific Health Impact Assessment', respectively. Furthermore, a keyword search on *pubmed* was conducted (see Table 7.1 for an overview). Finally, an extensive review of grey literature and relevant homepages was carried out to account for the applied

nature of HIA.¹

Table 7.1: Hits for the *pubmed* search conducted on 13. Feb. 2008.

Database	Term	Hits
pubmed	'health impact assessment' and 'simulation'	3
pubmed	'health impact assessment' and 'mode*ing'	5
pubmed	'health impact assessment' and 'quantitative'	11
pubmed	'health impact assessment' and 'simulation'	3
pubmed	'health impact assessment' and 'model'	17
pubmed	'health impact assessment' and 'software'	3
pubmed	'health impact assessment' and 'prediction'	6
pubmed	'health impact assessment' and 'projection'	7
		Total hits: 55
		40 excl. dupli- cate hits

7.2 Evaluating Existing Models

In Table 7.2 we describe each reviewed model in terms of the developed criteria of section 2.3. Many models are not publicly available and only limited descriptions exist. Furthermore, some models are ongoing projects, making it difficult to obtain up-to-date information. Hence, this is a tentative overview, where the greatest uncertainties are marked with a question mark. Furthermore, we undertook a detailed review of selected models used for HIA. This review only includes models that meet the three following criteria:

¹A problem is to distinguish were simply a methodology was applied versus the use of an actual simulation tool. We refrain from the inclusion of application of standard statistical method such as regression or just individual quantitative studies (for an excellent overview of quantitative studies within the HIA framework compare [Veerman et al. 2005]).

SECTION 7. APPENDIX B: REVIEW OF EXISTING MODELS

1. generic disease model with risk factor exposure
2. modeling of a general (and not patient-level) population
3. yields population health measure to have comparable outcomes

These are namely:

- ARMADA
- POHEM
- PREVENT
- RIVM-CDM
- Foresight Obesity Project

Table 7.2: Applying criteria to reviewed models I

Model	publicly available	heterogeneous	dynamic or static	epidemiologic model	generic	outcome measures	real population	model type	uncertainty
<i>ARMADA</i>	no	sex and age groups	dynamic	explicit risk states	yes	increased (or decreased) mortality and morbidity by cause	yes	dynamic life table	no
CHD Model	yes	sex	static	no risk factors	no	prevalence (of CHD)	yes	life table (?)	partly
ECOS/HECOS	no (?)	sex and age groups	(partly) dynamic	explicit risk states (?)	no (smoking)	LY (?), number of death prevented	yes	life table	No
<i>Foresight Obesity 2</i>	no	micro	dynamic	?	no	only bmi as risk factor	yes	ISM	the simulation part
GBD/DisMod	yes	sex and age groups (DisMod)	DisMod is dynamic/GBD is a method	no explicit risk state	yes	DALY		life table /PAR	no
Heat Cy-cling	yes	population as a whole	static	no explicit risk state	no (cycling)	number of lives saved	no		no
Hypertension Model	yes	sex, age, and ethnicity groups	static	no risk factors	no	prevalence (of hypertension)	no	life table	no
IMPACT	no	yes	static	yes	no (heart disease)	death prevented	yes	deterministic, cohorts in excel	no
INTARESE	no	infants, adults, and elderly	dynamic	no explicit risk state	no (pollution)	LE		life table	Yes (incl. model uncertainty)

Table 7.3: Applying criteria to reviewed models II

Model	publicly available	heterogeneous	dynamic or static	epidemiologic model	generic	outcome measures	real population ?	model type	uncertainty
MISCAN	no	micro	dynamic	?	no (screening)	yes	yes	DES	yes
PIAMOD/ MIAMOD	yes	sex and age groups	dynamic	no explicit risk state	no (cancer)	Incidence and Mortality estimates	?	Age-Period-Cohort and life table	yes (in the regression model)
POHEM	no	individual	dynamic	unlimited risk states	yes	yes	yes	DES	yes (in parameters)
POPMOD	yes	sex and age groups	dynamic	no explicit risk state	yes (two interacting diseases)	HLY, DALE	yes	life table	yes
PREVENT (?)		sex and age groups	dynamic	Par/Pif	yes	LE, DALE, costs	?	dynamic life table	no
MSLT	yes	sex and age groups	static	Par/Pif	yes	LE, DALE, DALY	no	period life table	no
Quit Benefits	no (?)	sex and age groups	static	Decision Tree	no	Incidence, DALE, no. of Death	no	Decision Tree based	no (but deterministic sensitivity analysis)
RIVM- CDM	no	sex and age groups	dynamic	explicit risk states	yes	HLY, DALE	yes	MSLT/Micro Sim	experimental option
SimSmoke	no longer (?)	sex, age, and ethnicity groups	dynamic	Par/Pif ?	life table no	smoking prevalence, number of death	yes		no (?)
UKPDS Outcomes Model	upon request	micro (patient level)	dynamic	no explicit risk state	no (diabetes)	DALE	no (patient level)	partial microsimulation	Yes

7.3 Vignettes for Selected Models

7.3.1 ARMADA - *Age Related Morbidity And Death Analysis*

Background: The ARMADA model has been devised by a research group at University College London. It was specifically designed to fit into the HIA framework. The declared objective of ARMADA is to "provide 'broad brush' population level estimates of likely changes in health relevant to the local population." The tool still seems to be under development and presently four publications describing it exist. It has been applied to the HIA of road traffic improvement and the long term effects of an incinerator site [McCarthy et al. 2002; McCarthy and Utley 2004].

Desiderata: The tool is not *publicly available* (currently, development seems to be dormant). The *heterogeneity of the population* is modeled at the cohort level differentiated by sex, age groups, and (environmental) risk status. It is *dynamic*, longer time horizons can be projected (e.g. 15 years in one example), and the projected figures are updated for every time step. The length of the time step, however, has to equal the age band of the population (and must be at least longer than 1 year). The *disease model* is based on a continuous Markov chain that is evaluated at discrete time intervals. This implies that health progression only depends on age, sex, current health status, and risk exposure. The chosen mathematical structure allows for dependent diseases

and risk factors and co-morbidity. It is a *generic disease* model, as there is no upper limit on the number of health conditions and environmental factors that can be included. The *outcome measures* are the increased (or decreased) mortality or morbidity for every age group and sex for every modeled disease. So far, no population level outcome measures – such as DALY – are implemented. A *real life population* can be modeled and population dynamics (such as birth) can be modeled as well.

Disease Model: The model is based on a continuous Markov chain. The population is divided by cohorts (based on sex and age group), and risk factor classes. In each of these sub-groups homogeneity is assumed. Hence, it is similar to the modeling of a *dynamic multi state life table*. The number of risk factors is F and within each risk factor there are X discrete states. Continuous risk factors are not possible, but there is no limit on the number of discrete classes. This means that there are X^F combinations of risk factors. Hence, risk factors are modeled explicitly and for every possible combination of risk factors, there is a single number r denoting this state. Similar, there are C health conditions and within these health conditions (diseases) there are p phases with $p = 1$ indicating the absence of the health condition and $p = P$ indicating death from this health condition. Hence, there are P^C different health states allowing every possible combination, denoted by the index number s . The advantages of this approach are that, as every combination of diseases is possible and their severity can be modeled, there is no need to assume independence between

diseases and every possible co-morbidity with every possible severity can be specified. One has to note, however, that some of these health states are nonsensical (such as dead from several diseases at once) and are not occupied. A baseline hazard B is specified, giving the rate of transition from phase $p = l$ to $p = k$ given a health condition. This baseline hazard has to be specified for every possible transition and depends only on age, sex, and risk factor state but not on duration of disease; duration could be modeled by increasing the number of disease states. The risk factors are included as multipliers, given a certain risk factor the baseline hazard is multiplied by a constant c , giving the increased or decreased risk of this particular risk factor (combination). The population state probability $Z(a, v, r, s, t)$ gives the probability/proportion of the population of age a with sex v in risk state r and health condition s at time point t . The comparison of Z_i (the simulation without the change in risk factor exposure) with Z_j (the simulation with the change in risk factor exposure) gives the difference in mortality and morbidity for the two different scenarios.

The disease model is able to model remission (returning from a severe health state to a less severe health state or being healthy) and chronic disease with an (in principle) unlimited number of progressions. Furthermore, partly acutely disease could be modeled as well. However, a disease where the mortality depends on the duration of disease can only be modeled through state progression. The transition between states is deterministic and *uncertainty* is not modeled.

Distinctive Features: Any combination of health states and risk factor exposure can be modeled (with increasing computing burden and data needs, however), hence there is no need to assume independence given enough data is available to calibrate the model and in particular the several baseline hazards. Only a disease process with discrete states can be modeled and time duration of a disease only within this framework. The effect of the risk factors on the transition is multiplicative. The length of the simulated time step must be longer than 1 year and equals the length of the age band. There are, so far, no population level based outcome measures but only differences in probability for morbidity and mortality by age group and sex. Uncertainty is not modeled explicitly

7.3.2 Proportional Multi State Life Table – MSLT

Background The proportional multi-state life table (MSLT) is rather a methodological approach than a self contained software tool for HIA. However, it has been used on several occasions – compare for example [Veerman et al. 2007] – for HIA and hence we decided to discuss it in more detail. The proportional MSLT has been developed by [Barendregt et al. 1998] to deal with multiple morbidity and examples for HIA applications include the health effects of fruit consumption and TV advertising for food products [Veerman 2007].

Desiderata: The proportional MSLT is implemented in a spreadsheet and, hence, no piece of software as such. A spreadsheet template is not *publicly*

available, but can be rather easily implemented in a standard spreadsheet program (e.g. Excel). The *heterogeneity of the population* is modeled at the cohort level differentiated by sex and age groups. The MSLT is static and allows for two different interpretations: either a single cohort that is followed from a specific age (usually birth) until the last member died or a population in a steady state. The usual interpretation is the latter one; however, from the MSLT one cannot infer when the steady state is reached or what trajectory is followed to reach it. The MSLT uses a *generic disease model* based on the PIF approach and the number of diseases that can be included is in principle not limited. It is cohort based and assumes homogeneity within a state defined by sex and age and disease. The *outcome measures* are differences in life expectancy, DALY, and disease-specific mortality rates for each disease by sex and age group. When the steady state interpretation is chosen, a *real life population* can be modeled, however, without any population dynamics.

Disease Model: The model is based on *period life table* with a disease model that uses the concept of population attributed risk (PAR) that attributes the incidence of a disease in a population to the intervention when the proportion of the exposed and the relative risk are known. Hence, risk factor states are not included. A short-coming of the PAR is that an intervention that reduces the exposure but does not eliminate it completely cannot be modeled. This is overcome using the potential impact fraction (PIF):

$$PIF = \sum \frac{(P_a - P'_a) \times (RR_a - 1)}{P_a \times (RR_a - 1) + 1} = \frac{\sum_a P_a \times RR_a - \sum_a P'_a \times RR_a}{\sum_a P_a \times RR_a}$$

The change in exposure P_a is used to calculate the reduction (or increase, depending on the size of the relative risk) in incidence of a given disease due to the intervention. The number of diseases is not limited and independence between the diseases is assumed (e.g. an increase in exposure leads to an increase in all incidences for the diseases affected by the respective risk). Two populations are simulated: the first with the baseline exposure and the second with the changed exposure due to the intervention. The population is usually divided into cohorts by sex and in one-year age intervals, but this depends on the available data. Risk factor states are not modeled and the change in exposure in the population ($P_a - P'_a$) must be determined exogenously to the model. In the applications of Veerman, a distributional assumption about the consumption of fruits and vegetables (the exposure) is made depending on a change in price. The MSLT has been used to model chronic diseases although remission can be included. The transition between states is deterministic and uncertainty is not modeled.

Distinctive Features: As the model is static, it cannot predict when a health gain is reached and it cannot identify redistribution of health gains between sub-groups of the population. The use of the PIF approach, which does not use explicit risk factor states, does not allow for mortality selection, but it has very modest data needs.

7.3.3 POHEM (*Population Health Model*)

Background POHEM is both an idea and a computer simulation model and has been developed by Michael Wolfson at Statistics Canada. Originally, it intended to provide a framework for understanding human health (data) and some of these concepts of the framework have been used to design the software tool of the same name. Three main goals of POHEM at its outset were to, first, calculate generalizations of life expectancy measures (such as healthy life expectancy), second, to provide coherence to health information data, and, third, to support decision making in regard to healthy-affecting interventions. Several applications exist already, mostly with Canadian data [Wolfson 1994].

Desiderata: POHEM is not *publicly available*, however, a library of programming tools (called MODGEN) used in the design of POHEM is available for download. The *heterogeneity of the population* can be specified to a very detailed level. Not merely age and sex structure, but POHEM also models life course events such as divorce and re-marriage. Furthermore, a host of socioeconomic variables and events can be specified such as income, educational attainment, labor force participation, child leaving home. POHEM is *dynamic* and models in *continuous time*. The *disease model* allows – in principle – for an unlimited number of states for a given disease or risk factor. Also the complexity of the causal pathway between the risk factors and diseases is not limited by the program. *Outcome measures* such as number of new cases,

death, and summary measures (e.g. LE, DALE) can be obtained for any time and at any detail of the population (e.g. age, sex, and SES). Furthermore, cost-effectiveness of interventions can be modeled and the level of health care utilization by the population as such or certain specified groups. A real life population including births and whole family structures can be modeled.

Disease Model: POHEM is a *discrete event simulation* (DES) and the epidemiological disease model is based on the concept of the next event: based on the characteristics of the individual the time to a next event is drawn. As POHEM models in continuous time the waiting time to all possible next events (such as contracting a disease or progressing within a disease state) is calculated. The event with the shortest waiting time is realized and then the waiting time for the next possible event, given the present state, is calculated. Diseases modeled with POHEM include coronary heart disease, lung cancer, breast cancer, and dementia. Examples for risk factors are radon, blood pressure, obesity, smoking and cholesterol (all potentially over the life course), with several socio-economic variables as confounders and other diseases as risk factors as well. This allows – in principal – for unlimited complexity. An additional layer of complexity is added by the possibility to simulate events affecting the socio economic characteristics, such as marriage or job loss. Two kinds of data is needed, first, knowledge about the risk (or probability) of an event given the characteristics of an individual, and, second, the characteristics of the simulated individuals itself. The disease model is able to model chronic

diseases, diseases with remission, partly actual disease, and diseases where the health states depends on the duration of having this disease. *Uncertainty* is modeled with uncertainty around the parameters (second order uncertainty), several distributional assumptions can be made and a multi-way probabilistic sensitivity analysis can be conducted.

Distinctive Features: The most distinctive feature of the POHEM model is that arbitrarily complex diseases can be modeled, co-morbidity and mortality selection are taken care of. However, this flexibility is limited not only by the knowledge about the disease process in question, but also by the available data. POHEM needs very rich, detailed data, preferably longitudinal, which is seldom available in Europe. For Canada, usually a survey is used that consists of over 100,000 records to simulate 2.4 million individual lives in a single run.

7.3.4 Foresight Obesity Project

Background The Foresight Obesity Simulation (FOS) was developed by Klim McPherson, Tim Marsh, and Martin Brown for the UK Government's Foresight project. FOS consists of two different modules. The first extrapolates trends of obesity and the second simulates the effects of these BMI distributions on several health conditions until the year 2050 [McPherson et al. 2007].

Desiderata: The program is not *publicly available* (and still under development). The first module predicts the levels of future obesity with a re-

gression model. The second module, the actual simulation, is *dynamic* and projects the development over time. It uses *discrete* time intervals of 5 years, the same length as the simulated age groups. The *population heterogeneity* for the prediction module allows sex, age, ethnicity, social class, and region. The simulation module differentiates by sex and age. The *disease model* uses only one risk factor (BMI), but several diseases affected by it are included. It seems, the simulations are done for each disease individually. *Outcome measures* are prevalence and incidence, life expectancy, and – most notably – disease costs. The total costs are the sum of the costs calculated for each individual diseases. A *real life population* is modeled and population dynamics seems to be included.

Disease Model: The aim of FOS is to assess the effect of obesity on population health. The first module predicts the prevalence of obesity by age group and sex until 2050. This is done for a continuous BMI, but the prevalence is expressed in 6 discrete BMI groups. The specified regression mode is able to accommodate the linear increase in some BMI groups observed between 1993 and 2004 without predicting a BMI group prevalence larger than 100 %. The second module is based on a *individual sampling model*, and simulates the change in BMI and incidence and prevalence of diseases for each individual. To ensure that the prevalence distribution of BMI in the population does not differ from the estimated trend the following equation is used:

$$F_{BMI}(b'|A_{k+1}, S, t + 5) = F_{BMI}(b|A_k, S, t)$$

An individual of sex S and age A will have a BMI of b' in the next time period ($t + 5$) with probability given by the solution of this equation. For the calculation of the incidence of a disease for a person in a given time interval, two probabilities are needed. The first, T_1 , is the probability of the person contracting the given disease if not overweight or obese. The second, T_2 , is the probability of the person contracting when overweight or obese (given his BMI group). The actual values for T_1 and T_2 depend on additional characteristics of the individual (such as age, gender, and disease history) and T_1 is smaller than T_2 . Now, a random probability p is drawn for each individual. If p is smaller than T_1 the person develops the disease, if p is larger than T_1 and smaller than T_2 the person is contracting the disease and his BMI is considered to be the cause, and if p is large than T_2 , the individual does not get the disease in this time step. The obesity related diseases are type-2 diabetes, coronary heart disease, stroke, arthritis, and obesity related cancer. Mortality is calculated using the RR based on BMI and does not take into account whether the individual is diseased or not. The risk of getting a disease does not depend on the presence of absence of any other diseases as those are modeled separately. *Uncertainty* is not modeled explicitly, however, an error analysis quantifying the errors of the BMI projection of module one and the variability

due to the nature of the micro simulation in module 2 is available. For the first part of the model (the regression based prediction of BMI prevalence) confidence intervals are readily available.

Distinctive Features: The program is still under development and the authors state the need to be tested and "validated more rigorously". An distinctive feature of the program is to project the distribution of the risk factor BMI independently from the simulation and use a mathematical structure to ensure that the simulated individuals follow the prescribed prevalence pattern over time.

7.3.5 PREVENT

PREVENT was developed by Jan Barendregt as a tool for policy makers in 1989 and is still ongoing work. The description is based on version 3. PREVENT models a dynamic population in which risk factors and diseases are embedded. It can model policy interventions by changing the prevalence of risk factors in the population [Gunning 1999; Barendregt nd, 1999].

Desiderata: The tool is not *publicly available* (and still under active development). It is implemented in a windows based software and requires MS-Access for the data input. The *heterogeneity of the population* is modeled at the cohort level, differentiated by ages and sex. It is *dynamic*, very long time horizons can be projected and the figures are updated for every time step (which have a length of one year). The *disease model* uses PIF and the change

of the prevalence due to an intervention within the population to determine the health effects. It is a *generic disease model* as different diseases can be modeled. In PREVENT, a disease can have multiple risk factors and risk factor can cause multiple diseases. Furthermore, a disease can be a risk factor for another disease. Several *output measures* exist by year, sex, and age, such as number of death or mortality rates. Furthermore, population level outcome measures exist such as life expectancy or years with disability. A *real life population* is modeled including birth and migration.

Disease Model: The disease model is basically a *dynamic life table* that uses the PIF methodology (see page 75). The user specifies the change in risk factor prevalence for a given age. Within this age group homogeneity is assumed. A limitation with specifying the risk factor prevalence for a given age is that PREVENT does not take into account mortality selection. The newest version of PREVENT allows for categorical and continuous risk factors prevalence (but not explicit risk factor states). The categorical risk factors need RR by category and the prevalence by category and year. For the continuous risk factors a distribution some statistical distribution can be specified (such as Normal, log-normal, or Weibull). Two simulations are run, first the baseline simulation and then the intervention simulation with the changes in risk factor prevalence (user specified) due to the intervention. The outcome measures are calculated by the difference of the two. The transition between states is deterministic and *uncertainty* is not modeled.

Distinctive Features: The user can specify a time until the intervention

starts to take effect and when it reaches full effect. This so called latency can be modeled with different distributions e.g. linear or exponential. Furthermore, the user can specify an autonomous trend of the incidence for a disease. The modeling at the cohort level does not allow for detailed population heterogeneity or mortality selection. PREVENT makes several independence assumptions, most notably for the distribution of risk factors, incidence rates, and disease specific cause of death. The effect of an intervention is specified for a certain age group and not for a cohort over time. The graphic output possibilities of PREVENT allow for a comfortable communication of the simulation results.

7.3.6 RIVM-CDM (Rijksinstituut voor Volksgezondheid en Milieu-Chronic Disease Model

Background: The RIVM CDM model has been devised by the RIVM (Netherlands) as a tool for studying the effectiveness of policies for primary prevention and to do burden of disease calculations in order to inform the Dutch Government of the current state of Public Health. In recent years use for cost-effectiveness analysis has become a major application. It has been applied to a broad range of policies such as interventions aimed at reducing smoking, increasing use of bicycles for transportation, supplying fruit to primary schools, effects of traffic noise and reduction of particular matter [Hoogenveen et al. 2005].

Desiderata: The tool is not *publicly available* (unassisted use is not feasible and the model is implemented in the commercial software Mathematica) and ongoing work. The *heterogeneity of the population* is modeled at the cohort level differentiated by sex, age groups, and risk factor status. It is *dynamic*, longer time horizons can be projected (no limit) and the projected figures are updated for every time step. The length of the time step is fixed at 1 year. Although here described as a single model, actually there are several different models. In principle all these models are based on a continuous Markov chain, comprising both the diseases and the risk factors, that is evaluated at different time (1-year) intervals. However, apart from the full Markov Model there is also an approximated version, called the "marginal model". The marginal model keeps track only of the marginal states, that is, for instance, the number of smokers in the population, or the number of persons with heart disease in the population. It does not keep track of the joined states (e.g. smokers with heart disease). Health progression in the model depends only on age, sex, current health status (= presence of diseases), and risk exposure. The chosen mathematical structure allows for dependent diseases and risk factors. It is a *generic disease model*, as in principle there is no upper limit on the number of health conditions and risk factors that can be included. The outcome measures are the increased (or decreased) risk factor prevalence, mortality or morbidity for every age group and sex for every modeled disease, life expectancy, health adjusted life expectancy (using DALY weights) and costs of health care. A

real life population can be modeled and population dynamics and immigration/emigration are modeled as well.

Disease Model: The model is based a on a continuous Markov chain. The population is divided by cohorts (based on sex and age group), and risk factor classes. In each of theses sub-groups homogeneity is assumed. Hence, it is similar to the modeling of a *dynamic multi state life table*. The number of risk factors is F and within each risk factor there are X^f discrete states. Continuous risk factors are not possible in the production version of the model, but there is not limit on the number of discrete classes. In this model risk factors are modeled explicitly and in the Full Markov Model for every possible combination of risk factors, there is a single number r denoting this state. In the marginal model, the distribution of the risk factors is assumed to be independent of each other, and thus can be calculated from the marginal distributions of each separate risk factor. Similar, there are C health conditions and within these health conditions (diseases) there are 2 phases with $p = 0$ indicating the absence of the health condition and $p = 1$ indicating the presence of this health condition. Hence, there are 2^C different health states allowing every possible combination, denoted by the index number s . Again, in the marginal model the joint states are calculated from the marginal states, taking conditional dependence based on common risk factors or dependencies between diseases into account. A baseline incidence rate B is specified, giving the rate of transition from phase $p = 0$ to $p = 1$ given that all risk factors are in the reference state (with relative risk =1 for the particular disease). For all other combination of

risk factor states, the incidence rate then is the baseline incidence rate multiplied by the relative risks that apply to the level of each risk factor. Relative risks depend on age, sex, and risk factor state but not on duration of disease. Effects of duration of disease have been model for diabetes by adding a disease progression indicator (HbA1c) as a risk factor to the model. Mortality is included as the sum of other cause mortality, acute disease mortality and disease attributable mortality. Disease attributable mortality depends on age and gender, but not on the duration of disease. The population state probability $Z(a,v,r,s,t)$ gives the probability/proportion of the population of age a with sex v in risk state r and health condition s at time point t . The comparison of Z_i (the simulation without the change in risk factor exposure) with Z_j (the simulation with the change in risk factor exposure) gives the difference in each outcome for the two different scenarios.

The disease model is able to model remission. Furthermore, partly acutely disease is be modeled as well. However, a disease where the mortality depends on the duration of disease is only modeled through disease progression markers (like lung function for COPD and HbA1c for diabetes). The transition between states is deterministic, but a micro-simulation variant is under construction. Uncertainty is included by offering the possibility to calculate elasticity coefficients, and an experimental option (that is, only for the relative risk parameters) for Monte-Carlo sensitivity analysis is available, while more extensive options are under construction.

Distinctive Features: For the Full Markov Model, any combination of diseases and risk factor exposure can be modeled. However, in practice the number of risk factors and diseases that can be included is limited due to computational limitation, and studying combinations of states demands having internally consistent data, which limits the use of the Full Markov model. Often assumptions are made for its use are similar to the assumptions used to construct the marginal model. The marginal model can handle any number of risk factors and diseases. The effect of the risk factors on transitions (both disease incidence and other cause mortality) is multiplicative, while the effect of diseases on mortality is additive. The length of the simulated time step is 1 year and equals the length of the age band. There are population level based outcome measures, and there are limited probabilities for modeling uncertainty. Furthermore, there are specific variants of the model that model disease progression in diabetes patients and COPD-patients.

7.4 Background on further Reviewed Models

This subsection gives some background information about the models reviewed. Please note that the descriptions are abridged excerpts taken from the respective article, the homepages, or manuals of the respective programs.

CHD Model The coronary heart disease (CHD) model is one of the prevalence models, developed on behalf of the Association of Public Health Observatories by the Yorkshire and Humber PHO and Eastern Region PHO to show the expected prevalence of disease in given geographies and user-defined populations (<http://www.apho.org.uk/resource/item.aspx?RID=48308>). Other examples are: the hypertension model (included in our review), the diabetes model and the mental illness model. The CHD model is designed for estimating the Primary Care Trust (PCT) level prevalence of patient-reported doctor-diagnosed CHD. The model uses data from English health surveys using self-reported doctor-diagnosed CHD which has been shown to be predictive of objective CHD, adjusted for PCT level deprivation.

GBD/DisMod DISMOD is a software tool to check the internal consistency of epidemiological estimates of incidence, prevalence, duration and case fatality for diseases (<http://www.who.int/healthinfo/boddismod/en/index.html>). DISMOD is available in two versions: DISMOD I and II. DISMOD II is a new software system developed to provide a full graphical interface, database storage capabilities and substantially enhanced features and options [Baren-

dregt et al. 2003b]. DISMOD I was used as an analytical tool in the WHO Global Burden of Disease 1990 study. Based on the experience of the users, it was decided to develop a new DisMod for the Global burden of Disease 2000 study that follows the same principles, but avoids some problems of the old DisMod and adds a number of new features. The conceptual model of DisMod II, like the original DisMod, is that of a multi-state life table. The model describes a single disease, together with mortality from all other causes. Healthy people, defined as people unaffected by the disease being modeled, are subject to an incidence hazard, and may become diseased. When diseased they are subject to a hazard of dying from the disease, the case fatality, and to a hazard of recovering from the disease (remission). Both, healthy and diseased people are subject to the same mortality hazard from all other causes. Because of a combination of analytical and numerical methods DisMod II accepts, in addition to the transition hazards incidence, remission and case fatality (or its equivalent relative risk for total mortality), the following disease input variables: incidence as a population rate (with total population in the denominator instead of person years at risk), prevalence, duration, and mortality.

ECOS/HECOS ECOS/HECOS is a tool (both web based and stand-alone), designed to estimate the health and economic outcomes associated with smoking and the benefits of smoking cessation on the population level [Antoñanzas and Portillo 2003; Orme et al. 2001]. HECOS models smoking behavior and associated mortality, morbidity, and health care costs. In the model, smokers

are at risk from smoking related diseases (chronic obstructive pulmonary disease, asthma, chronic heart disease, stroke, lung cancer, and low birth weight pregnancies) and may die prematurely as a result. Ex-smokers can also acquire smoking related diseases, but their risk of disease will be less than that of a current smoker. Death from non-smoking related causes are not captured in the model. The smoking status of an individual in the model can be split into three discrete (non-overlapping) states, namely: current smoker, recent quitter, and long-term quitter. Furthermore, the health status of an individual can also be split into three mutually exclusive states, namely: no morbidity (healthy), morbidity (not healthy but alive), and dead. Altogether, an individual can be in one of seven model states according to the smoking and health status of that individual. The transition from one state to another is determined by the rate at which smoking behavior changes (that is, quit rates and relapse rates), as well as disease and mortality rates (from smoking related causes).

To model the effect of smoking cessation, the interface runs two parallel calculations. In the first year of the model, one calculation moves a number of smokers from the recent quitters state to the long-term quitters state, according to the efficacy of the smoking cessation strategy chosen. The parallel calculation assumes that the smoking cessation strategy did not take place. The results in subsequent years are then compared to ascertain the benefit of the incremental smoking cessation, which took place in the first year. This approach takes into account those who would have quit smoking anyway, and those who would have subsequently relapsed.

Heat Cycling The health economic assessment tool for cycling (HEAT for cycling) the economic savings resulting from reduced mortality due to cycling (http://www.euro.who.int/transport/policy/20070503_1). For example if x people cycle y distance on most days, what is the economic value of the improvements in their mortality rate? HEAT for cycling can be applied in many situations, for example:

- When planning a piece of new cycle infrastructure, it allows the user to model the impact of different levels of cycling, and attach a value to the estimated level of cycling when the new infrastructure is in place. This can be compared to the costs to produce a cost-benefit ratio (and help make the case for investment), or as an input into a more comprehensive cost benefit analysis;
- To value the mortality benefits from current levels of cycling, such as to a specific workplace, across a city or in a country;
- To provide input for more comprehensive cost-benefit. analyses.

Hypertension Model The hypertension model is one of the prevalence models, developed on behalf of the Association of Public Health Observatories by the Yorkshire and Humber PHO and Eastern Region PHO to show the expected prevalence of disease in given geographies and user-defined populations (<http://www.apho.org.uk/resource/item.aspx?RID=48308>). Other examples are: the coronary heart disease model (included in our review), the diabetes model, and the mental illness model. The hypertension model aims to produce Primary Care Trust (PCT) level prevalence estimates for hyper-

tension. The estimated number of persons with hypertension is derived by multiplying PCT registered populations by hypertension prevalence rates from Health Surveys from England, adjusted for ethnicity. The model builds upon an existing model developed by the Faculty of Public Health Medicine, which did not include an adjustment for ethnicity.

IMPACT IMPACT is a cell-based, deterministic model originally developed to quantify the effects of improved treatments and population risk factor changes on trends in CHD-mortality [Ford et al. 2007]. It compares two time points in the past. It uses mortality rates from the first time point and applies it to the second time point to calculate the difference, the number of death prevented or postponed (DPP). To model the DPP attributable to a specific treatment, the number of patients in a given age-sex stratum is multiplied with the proportion of patients actually getting this treatment, the 1-year-case-fatality rate, and the relative reduction of the 1-year-case fatality rate. For risk factors such as blood pressure a similar procedure is used. IMPACT has also been used for future predictions in the UK, Ireland and the USA. (Personal Communication Simon Chapewell)

INTARESE The INTARESE model is based on a life table and assesses the population effect of a reduction in overall pollution levels [Tainio et al. 2007]. It is part of the INTARESE project (<http://www.intarese.org/>). The main focus of the project is the estimation of parameters measuring the mortality stemming from pollution. The life table model predicts life-expectancy (LE)

and monetary value of lost life years. The LE was predicted by defining the change in the background hazard rate caused by local-traffic-related primary fine particles. The time difference between an exposure and the consequent health effects (lag) was included in the model. The monetary value of life-year-lost was predicted by calculating a value for a life year and discounting the future benefits and costs.

MIAMOD and PIAMOD MIAMOD and PIAMOD are statistical methods, developed by researchers from the Istituto Superiore di Sanita (National Institute of Health, Rome, Italy) to estimate and project cancer incidence and prevalence both at regional and national level (<http://www.eurocare.it/Miamod/Miamod.htm>). The MIAMOD method (*Mortality and Incidence Analysis MODel*) has been first proposed [Angelis et al. 1994]. It involves modeling incidence as an age, period, and cohort (APC) function and back-calculating its parameters from cancer mortality and survival. Both observed data and model-based survival estimates can be used. Based on APC estimated parameters, incidence is projected into past and future years. Prevalence is derived from estimated and projected incidence by convolution of cancer incidence and survival over time. The PIAMOD (*Prevalence and Incidence Analysis MODel*) method is an alternative to MIAMOD for estimating and projecting prevalence when incidence data are available, i.e. on the areas covered by cancer registration. In PIAMOD observed incidence is directly modeled as an APC model. Prevalence is derived, as in MIAMOD method,

from the convolution of cancer incidence and survival over time.

MISCAN The MISCAN computer simulation program has been developed for building models for cancer screening in a dynamic population, and for subsequently applying these models to analyze and explain results of cancer screening trials, to predict and compare the (cost-) effectiveness of different screening policies, and to monitor the results of population screening programs [Habbema et al. 1985] (https://cisnet.flexkb.net/mp/pub/cisnet_breast_erasmus_profile.pdf#pagemode=bookmarks). Several variants of the MISCAN model have been made and applied for cancer of the cervix, breast, colon, and prostate. The MISCAN models use discrete event based micro simulation: using the model inputs, independent life histories are generated including a possible cancer history and the effects of treatment and early detection by screening. In the standard MISCAN models, the natural history is described by defining discrete tumor stages, transition probabilities between these stages, and dwelling times in each stage. In a more recent variant, MISCAN-Fadia, a more biologically oriented continuous tumor growth component as an alternative for the standard discrete stage natural history and screening component in MISCAN is used.

POPMOD PopMod simulates the evolution in time of an arbitrary population subject to births, deaths and two distinct disease conditions (http://www.who.int/choice/toolkit/pop_mod/en/index.html). The model population is segregated into male and female subpopulations, in turn segmented

into age groups of one-year span. Each age-and-sex specific population group is subdivided into four distinct states representing disease status. The four states comprise two groups with specific disease conditions, a group with the combined condition and a group with neither of the conditions. The states are denominated for convenience X, C, XC, and S, respectively. Disease state entirely determines health status and disease and mortality risk for its members. PopMod simulates the time evolution of the population by means of a system of ordinary differential equations. Basic PopMod output consists of the size of the population age-sex groups reported at yearly intervals. From this output further information is derived. Estimates of the severity of health states are required for full results, which include standard life-table measures as well as a variety of other summary measures of population health, which include standard life-table measures as well as a variety of other summary measures of population health. PopMod enables the analyst to model the incidence / prevalence, remission and case-fatality associated with a given disease or risk factor, both under the situation of no health care and also under the situation of one or more effective interventions being in place (at a specified level of coverage) [Lauer et al. 2003]. In order to estimate the population-level impact of different health interventions, the population model PopMod tracks a whole population (such as a whole country or WHO sub-region) over a period of 100 years. In this way, it is possible to establish the population-level health gain (or disease burden averted) as a result of a given intervention, relative to doing nothing.

SimSmoke The SimSmoke tobacco control simulation model projects smoking rates and deaths attributable to smoking (in total and for lung cancer, COPD, heart, and stroke), and examines the effect of tobacco control policies on those outcomes [Levy nd; Levy et al. 2000] (http://www.tobaccoevidence.net/pdf/sea_activities/SimSmoke_asean.pdf). The model can be used to examine the effect of policies individually and in combination on different ages and other demographic groups. The model can be used for predictive/planning purposes, justification of policies individually or as part of a comprehensive tobacco control program, and to help facilitate understanding of the role of tobacco control policies and how they may be most effectively implemented. SimSmoke is developed in 3 parts:

- 1) The Population Module in which the population evolves through births and deaths,
- 2) The Smoking Module distinguishes smokers, never smokers and 6 categories of ex-smokers, and these numbers evolve based on initiation and cessation rates, and death rates of smokers and ex-smokers relative to never smokers
- 3) Individual Policy Modules (taxes, clean air laws, media campaigns, cessation treatment programs and youth access enforcement) which translates the effect of policies implemented in different ways on smoking rates. Currently, the model distinguishes the population by age, gender and racial ethnic groups represented (White, African American, Hispanic, Asian and other), and predicts smoking rates and deaths for each of the demographic groups. The age, gender and especially racial/ethnic groups in the model can be adjusted as rel-

evant to the important socio-demographic demographic differences and data availability of other nations.

Quit Benefits (QBM) The Quit Benefits Model (QBM) is a Markov model, programmed in TreeAge Pro, that assesses the consequences of quitting smoking in terms of cases avoided of the four most common smoking-associated diseases (acute myocardial infarction (AMI), stroke, lung cancer, and chronic obstructive pulmonary disease (COPD)), deaths avoided, and quality-adjusted life-years and health care costs saved [Hurley and Matthews 2007]. The model works as follows: at the beginning of the analysis period, all subjects (smokers and quitters) are assumed to be in the health state "Well". During each subsequent one year period (or cycle) simulated subjects can either stay in the health state "Well", or, if one of the four smoking-related illnesses is diagnosed they move (transition) to the corresponding health state "Stroke year 1", "Lung Cancer year 1", "AMI year 1", or "COPD". If a subject dies, they move to the health state "Dead". Subjects who develop COPD are assumed to either stay in that state or die during subsequent cycles. The model is more complex for the other three smoking-associated diseases to reflect the fact that either the probabilities of death, or costs, or both, varied between or within subsequent cycles. The following outcomes can be assessed separately for male and female smokers and quitters, for various ages of quitting smoking, with different durations of follow-up and different discount rates for future benefits: Incidence of four diseases, total deaths, including deaths attributable to all

smoking-related diseases, and deaths due to the above four diseases, life expectancy and Quality-adjusted life-expectancy (QALE). Quality adjustments to life-expectancy were made based on the reduced utility of life associated with each of the four specified smoking-related diseases.

UKPDS Outcomes Model The UKPDS Outcomes Model is a computer simulation model for estimating the long-term impact of health interventions for people with type 2 diabetes [Clarke et al. 2004] (<http://www.dtu.ox.ac.uk/OutcomesModel/UKPDSOutcomesManual.pdf>). It has been developed primarily to assess the lifetime benefits of diabetes-related interventions. In particular, it is intended to facilitate economic evaluations by estimating changes in outcomes such as life expectancy and quality adjusted life expectancy, when risk factors such as blood glucose level, blood pressure, lipid levels and smoking status are changed. The UKPDS Outcomes Model uses a wide variety of input data, including knowledge of previous events for individuals, and has the ability to take into account changes in some risk factor levels over time. The UKPDS Outcomes Model outputs are estimated Life Expectancy and Quality Adjusted Life Expectancy for each member of a given population. It can be applied to any population with type 2 diabetes.

Bibliography

- G. de Angelis, R. de Angelis, L. Frova, and A. Verdecchia. Miamod: a computer package to estimate chronic disease morbidity using mortality and survival data. *Computer Methods and Programs in Biomedicine*, 44(2):99–107, 1994.
- F Antoñanzas and F Portillo. [economic evaluation of pharmacotherapies for smoking cessation]. *Gaceta sanitaria / S.E.S.P.A.S*, 17(5):393–403, 2003.
- J. J. Barendregt. Prevent – the technical background. In C. A. Baan, J. J. Barendregt, Luc Bonneux, H. Bronnum-Hansen, Louise Gunning-Schepers, Kamper-Jorgensen, Paul van der Maas, and et al., editors, *Public health models: tools for health policy making at national and European level*, pages 17–31. UvA, Amsterdam, 1999.
- J. J. Barendregt, G. J. van Oortmarssen, van Hout Ben A., Jacqueline M. van den Bosch, and Luc Bonneux. Coping with multiple morbidity in a life table. *Mathematical Population Studies*, 7(1):29–49, 1998.
- Jan Barendregt, Gerrit van Oortmarssen, Theo Vos, and Christopher Murray. A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. *Population Health Metrics*, 1(1):4, 2003a.
- Jan Barendregt, Gerrit van Oortmarssen, Theo Vos, and Christopher Murray. A generic model for the assessment of disease epidemiology: the computational basis of dismod ii. *Population Health Metrics*, 1(1):4, 2003b.
- Jan J. Barendregt. Prevent v 3.0: Work in progress, nd. Presentation.
- Joerg Becker, Bjoern Niehaves, and Karsten Klose. A framework for epistemological perspectives on simulation. *Journal of Artificial Societies and Social Simulation*, 8(4):1, 2005.

BIBLIOGRAPHY

- S. C. Brailsford. Overcoming the barriers to implementation of operations research simulation models in healthcare. *Clinical and Investigative Medicine*, 28(6):321–315, 2005.
- Paul Bratley, Bennett L. Fox, and Linus E. Schrage. *A guide to simulation*. Springer, New York, Berlin, 1987.
- Alan Brennan, Stephen E. Chick, and Ruth Davies. A taxonomy of model structures for economic evaluation of health technologies. *Health Economics*, 15(12):1295–1310, 2006.
- A.H. Briggs. Handling uncertainty in cost–effectiveness models. *Pharmacoeconomics*, 17:479–500(22), 2000.
- Andrew Briggs, Karl Claxton, and Mark Sculpher. *Decision modelling for health economic evaluation*. Handbooks in health economic evaluation series. Oxford Univ. Press, Oxford, 2006.
- H. Bronnum-Hansen. How good is the prevent model for estimating the health benefits of prevention? *J. Epidemiol Community Health*, 53(5):300–305, 1999.
- Martin J Buxton, Michael F. Drummond, Ben A. van Hout, Richard L. Prince, Trevor A. Sheldon, Thomas Szucs, and Muriel Vray. Modelling in economic evaluation: An unavoidable fact of life. *Health Economics*, 6(3):217–227, 1997.
- P.M. Clarke, A.M. Gray, A. Briggs, A.J. Farmer, P. Fenn, R.J. Stevens, D.R. Matthews, I.M. Stratton, and R.R. (On behalf of the UK Prospective Diabetes StudyGroup) Holman. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the united kingdom prospective diabetes study (ukpds) outcomes. *Diabetologia*, 47(10):1747–1759, 2004.
- B. L. Cole and J. E. Fielding. Health impact assessment: A tool to help policy makers understand health beyond health care. *Annual Review of Public Health*, 28:393–412, 2007.
- D. Commenges. Multi–state models in epidemiology. *Lifetime Data Analysis*, 5(4):315–327, 1999.

BIBLIOGRAPHY

- Earl S. Ford, Umed A. Ajani, Janet B. Croft, Julia A. Critchley, Darwin R. Labarthe, Thomas E. Kottke, Wayne H. Giles, and Simon Capwell. Explaining the decrease in u.s–deaths from coronary heart disease, 1980–2000. *The New England Journal of Medicine*, 356:2388–2398, 2007.
- Marthe R. Gold, David Stevenson, and Dennis G. Fryback. HALYS and QALYS and DALYS, OHMY: Similarities and differences in summary measures of population health. *Annu. Rev. Public Health*, 23:115–134, 2002.
- Louise J. Gunning. Introduction to the biomed project. In C. A. Baan, J. J. Barendregt, Luc Bonneux, H. Bronnum-Hansen, Louise Gunning-Schepers, Kamper-Jorgensen, Paul van der Maas, and et al., editors, *Public health models: tools for health policy making at national and European level*, pages 7–15. UvA, Amsterdam, 1999.
- J. D. F. Habbema, J. J. Barendregt, and R. Boer. Chronic disease modeling: Draft for the encyclopedia of public health. In Kris Heggenhougen and Stella Quah, editors, *International Encyclopedia of Public Health*. Academic Press, in press.
- J.D.F. Habbema, G.J. van Oortmarssen, J.Th.N. Lubbe, and P.J. van der Maas. The miscan simulation program for the evaluation of screening for disease. *Computer Methods and Programs in Biomedicine*, 20(1):79–93, 1985.
- Michael T. Halpern, Bryan R. Luce, Ruth E. Brown, and Bernard Geneste. Health and economic outcomes modeling practices: A suggested framework. *Value in Health*, 1(2):131–147, 1998.
- Rudolf Hoogenveen, T. L. Feenstra, Pieter Baal, and C. A. Baan. A conceptual framework for budget allocation in the rivm chronic disease model – a case study of diabetes mellitus: Rivm rapport. Bilthoven, 2005.
- Susan Hurley and Jane Matthews. The quit benefits model: a markov model for assessing the health benefits and health care cost savings of quitting smoking. *Cost effectiveness and resource allocation*, 5(1):2, 2007.
- Jonathan Karnon. *Economic Evaluation of Health Care Technologies: A Comparison of Alternative Decision Modelling Techniques: PhD-thesis*. PhD thesis, Brunel University, 2001.

BIBLIOGRAPHY

- J. Kemm. What is hia and why might it be useful? In Matthias Wismar, Julia Blau, Kelly Ernst, and Josep Figueras, editors, *The Effectiveness of Health Impact Assessment. Scope and limitations of supporting decision-making in Europe*, European Observatory on Health Systems and Policies, pages 3–13. WHO, 2007.
- Michelle E. Kruijshaar, J. J. Barendregt, and N. Hoeymans. The use of models in the estimation of disease epidemiology. *Bulletin of World Health Organization*, 80:622–628, 2002.
- Jeremy Lauer, Klaus Rohrich, Harald Wirth, Claude Charette, Steve Gribble, and Christopher Murray. Popmod: a longitudinal population model with two interacting disease states. *Cost effectiveness and resource allocation*, 1(1):6, 2003.
- Averill M. Law and W. David Kelton. *Simulation modeling and analysis*. McGraw–Hill series in industrial engineering and management science. McGraw–Hill, Boston, 3. ed. edition, 2000.
- David Levy. Application of simsmoke to other nations. manuscript, nd.
- David T. Levy, K. Michael Cummings, and Andrew Hyland. A simulation of the effects of youth initiation policies on overall cigarette use. *American Journal of Public Health*, 90(8):1311–1314, 2000.
- Karen Lock and Martin McKee. Health impact assessment: assessing opportunities and barriers to intersectoral health improvement in an expanded european union. *J Epidemiol Community Health*, 59(5):356–360, 2005.
- M. McCarthy, J. P. Biddulph, M. Utley, J. Ferguson, and S. Gallivan. A health impact assessment model for environmental changes attributable to development projects. *J Epidemiol Community Health*, 56(8):611–616, 2002.
- Mark McCarthy and Martin Utley. Quantitative approaches to health impact assessment. In John Kemm, Jayne Parry, and Stephen Palmer, editors, *Health Impact Assessment: Concepts, Theory, Techniques and Applications*. OUP, Oxford, 2004.
- Klim McPherson, Tim Marsh, and J. Brown. Tackling obesities: Future choices – modelling future trends in obesity and the impact on health: Foresight. London, 2007.

BIBLIOGRAPHY

- J. Mindell, E. Ison, and M. Joffe. A glossary for health impact assessment. *J Epidemiol Community Health*, 57(9):647–651, 2003.
- Michelle E. Orme, Susan L. Hogue, Lisa M. Kennedy, Abigail C. Paine, and Christine Godfrey. Development of the health and economic consequences of smoking interactive model. *Tob Control*, 10(1):55–61, 2001.
- J. M. Parry and J. Wright. Community participation in health impact assessments: intuitively appealing but practically difficult. *Bulletin of World Health Organization*, 81(6):388, 2003.
- J. M. Parry, J. R. Kemm, and on behalf of all participants of the Evaluation of Health Impact Assessment Workshop. Criteria for use in the evaluation of health impact assessments. *Public Health*, 119(12):1122–1129, 2005.
- Zoe Philips, Laura Bojke, Mark Sculpher, Karl Claxton, and Su Golder. Good practice guidelines for decision-analytic modelling in health technology assessment: A review and consolidation of quality assessment. *Pharmacoeconomics*, 24(4):355–371, 2006.
- Project-Group. European policy health impact assessment, a guide, 2004.
- Bjarne Robberstad. Qalys vs dalys vs lys gained: What are the differences, and what difference do they make for health care priority setting? *Norsk Epidemiologi*, 15(2):183–191, 2005.
- Mark Sculpher, Elisabeth Fenwick, and Karl Claxton. Assessing quality in decision analytic cost-effectiveness models: A suggested framework and example of applications. *Pharmacoeconomics*, 17(5):461–477, 2000.
- Martin Spielauer. Dynamic microsimulation of health care demand, health care finance and the economic impact of health behaviours: survey and review. *International Journal of Microsimulation*, 1(1):35–53, 2007.
- Marko Tainio, Jouni Tuomisto, Otto Hanninen, Juhani Ruuskanen, Matti Jantunen, and Juha Pekkanen. Parameter and model uncertainty in a life-table model for fine particles (pm2.5): a statistical modeling study. *Environmental Health*, 6(1):24, 2007.
- J. L. Veerman. *Quantitative health impact assessment: an exploration of methods and validity*. PhD thesis, Erasmus University, Rotterdam, 2007.

BIBLIOGRAPHY

- J. L. Veerman, J. J. Barendregt, and J. P. Mackenbach. Quantitative health impact assessment: current practice and future directions. *J. Epidemiol Community Health*, 59(5):361–370, 2005.
- J. Lennert Veerman, Johan P. Mackenbach, and Jan J. Barendregt. Validity of predictions in health impact assessment. *J Epidemiol Community Health*, 61(4):362–366, 2007.
- Milton C. Weinstein, Bernie O’Brien, John Hornberger, Joseph Jackson, Magnus Johannesson, Chris McCabe, and Bryan R. Luce. Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR task force on good research practices. *Value in Health*, 6(1):9–17, 2003.
- Frans Willekens. Continuous-time microsimulation in longitudinal analysis: Netherlands interdisciplinary demographic institute (nidi). Manuscript, July 2007.
- Michael C. Wolfson. Pohem – a framework for understanding and modelling the health of human populations. *World Health Statistics Quarterly*, 47(3–4):157–176, 1994.
- World-Health-Organization. Health impact assessment: main concepts and suggested approach.: Gothenburg consensus paper, 1999.
- Binbing Yu, Ram C. Tiwari, Kathleen A Cronin, and Eric J. Feuer. Cure fraction estimation from the mixture cure models for grouped survival data. *Statistics in Medicine*, 23(11), 2004.