Roads to health

multi-state modelling of population health and resource use
Cover illustration
Title: “Abode hut and main frame computer”; pencil drawing by author, age 15. The left
two-thirds of the drawing depicts the developing world; the right side represents the
developed world.

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PREFACE

My initiation into health research took place when I entered Erasmus medical school. I had been attracted by it’s ‘Querido concept’ aiming for a synthesis of scientific insights and medical practice. This resulted in a first publication in neuroscience. As a graduate, I struggled with Tanahasi’s papers on the assessment of health services and on health & development. This book, my doctorate thesis, is a milestone on the same road.

I thank Frans Willekens and Frans Rutten for trust, opportunity, and guidance. As their disciplines are completely interwoven in this thesis, I wish that Dutch universities would facilitate joint doctorates. Frans W, introducing the topic, I proposed to finish in three years. The inspirational sessions with you and your group made me finish in due time i.e. twice as long as planned. Your methodological and international experience contributed essentials. Frans R, without knowing we have been on the same road: you started MTA at Erasmus when I studied health economics at LSE. I thank you also for the chance to expand its horizons. I thank the committee members for reading the manuscript. Amidst studies and projects, I met special people contributing to my rebirth from a young, angry clinician into a thoughtful researcher. Hans Valkenburg at medical school shared the orientation on both developing and developed countries. As an enlightened epidemiologist, he was the first to point out to me the potential of health modelling. Brian Abel-Smith and George Cumper in London showed me how health economics blends with public health. Jan Barendregt and Luc Bonneux at Erasmus are kindred souls. Bert de Vries and Rudolf Hoogenveen at the National Institute made me keep my sense of direction. Ben van Hout at Erasmus had answers to my questioning, leaving room for my own. I thank these ‘maestros’ for sharing their insights, each in a unique way.

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My neglected friends, I am back again from an interesting trip. My biggest smile is for my deceased parents. They are watching me from somewhere inside of me, proud in their own way. Willem, brother, I am happy you can share this book with me. Silvia, inspiring for decades, I dedicate the Mexico study to you. Hanne, Tijs, and Marre, my dearest, may you always be there like you have been during my writing. Hilde, the last words are for you: “Jungle deep, mountain high!”

Mijn verwaarloosde vrienden, ik ben weer terug van een interessante reis. Mijn grootste glimlach is voor mijn overleden ouders. Van ergens in mij zijn ze me blijven observeren, trots, op hun eigen manier. Willem, broer, ik ben blij dat ik dit boek met je kan delen. Silvia, inspirerend door de jaren heen, ik draag de Mexico studie aan jou op. Hanne, Tijs en Marre, mijn allerliefsten, mogen jullie er altijd zijn, net zoals jullie tijdens het schrijven er altijd geweest zijn. Hilde, de laatste woorden zijn voor jou: “Jungle deep, mountain high!”

Rotterdam, June 2002
PART I

INTRODUCTION
CHAPTER 1

THE LIFETIME APPROACH TO POPULATION HEALTH MODELLING

1.1. SUMMARY

Introduction This book describes changing disease occurrence in populations in various stages of socio-economic development, using integrated multi-state modelling techniques. These techniques analyse population health and health care costs during a lifetime under the influence of changes in health determinants, accounting for multiple diseases and multiple health determinants. Two kinds of determinants are distinguished: macro-determinants, such as income status, literacy, availability of food and water, and health services, and micro-determinants, such as smoking, other health risks and specific health interventions.

Methods The first chapter gives a typology of integrated multi-state modelling. It describes how one uses a causal framework to arrive at the definition of a multi-state model starting from the research question. Next, it explains how a model can be used to describe, explain, and simulate changing occurrence of diseases in a lifetime. This is in terms of disease incidence, survival, and resulting prevalence, distinguishing single or multiple disease stages. Additional mathematical explanatory models are applied to quantify changes in incidence and disease survival due to changes in health determinants, including those attributable to medical interventions.

Results A general outline of a comprehensive approach to population health is given, accounting for all of its main determinants. The outline specifies the chosen model approach in terms of point estimates and value distributions for states and flows. It shows how uncertainty in input distributions can account for uncertainties in model results. Results are defined in terms of health effects and medical costs, both as intermediate and aggregate outcomes.

Conclusion The chapter formulates the general research questions of how to assess changes in population health due to medical interventions and how to optimise the use of resources. These questions may need comparative analyses of important options in prevention and treatment. The questions usually can be grouped into two categories: “How exactly would the intervention influence population health?” and “What are effective and efficient ways to reduce disease and death at the population level?” The first postulate in the chosen approach is that the changes in population health under the influence of health determinants can be described more adequately in a dynamic disease-specific way. The second research postulate is that some “roads to health” may lead to health more quickly and at the expense of fewer resources than other roads. Given the scarcity of resources and the increased demand, there is a need for methods to describe and to determine optimal pathways to maintain and increase present health levels.
1.2. APPROACHES IN INTEGRATED HEALTH MODELLING

This book describes the changing disease occurrence in populations in various stages of socio-economic development, based on integrated multi-state modelling techniques. These techniques can be used to analyse population health and health care costs under the influence of changes in health determinants. Two kinds of determinants are distinguished: macro-determinants, such as income status, food, water and health services, and micro-determinants, such as smoking, other specific risks, and health interventions. Multi-state modelling is used to describe, explain, and simulate changing occurrence of multiple diseases in populations. Disease occurrence is described in terms of incidence, survival and resulting disease prevalence, distinguishing single or multiple severity stages. Additional mathematical explanatory models are applied to quantify changes in incidence and disease survival due to changes in health determinants, including those attributable to medical interventions. First, this chapter summarises the existing integrated model approaches. Next, it introduces multi-state health modelling, giving a typology of this approach. Its aim is to highlight some innovations, giving some typical examples, and to guide the reader through the subsequent chapters. The population health problems to be addressed and the generic methodology developed are explained in chapters 2 and 3. The following three chapters give a number of applications in the fields of epidemiology and health economics.

Health policies to improve population health need information on the level of diseases and the relative contribution of underlying causes. There are many theoretical frameworks explaining the distribution of health and illness in populations in terms of health determinants (Niessen et al., 2000). The boundaries of these frameworks depend very much on the breadth and scope of the health policy strategy. In most overall causal conceptual frameworks, broad health determinants are identified like literacy and income status and more proximate determinants like the classical health risks and nutritional status distribution (McNeil, 1976; Christian B, 1977; VWS, 1986; Frenk et al., 1993; Vallin, 1992; Hurowitz, 1993; Ruwaard et al., 1993; Murray et al., 1993a-c; Bobadilla, 1993).

Most of these approaches are formulated at the conceptual level only. Some are translated into mathematical representations. The translation process obliges the analyst to make the underlying assumptions explicit, quantifiable, and refutable. In this respect, mathematical health modelling does not differ from any other type of medical research. There are a number of modelling approaches in health such as in medical statistics (using empirical data sets), in clinical decision making (based on decision trees), to support the infectious disease control (accounting for transmission dynamics) and in epidemiology and demography (single disease models). The focus of the present study is on health at the population level accounting for multiple diseases and multiple determinants. Its methodology, although comparable to the former approaches, is grounded in sciences that study public health: epidemiology, demography, and health economics. Multi-sectoral regression models are familiar and are based on existing data sets. These analyse the
combined influences of various sectors of society i.e. gross national product, food and water supply, sanitation and education and medical services. (Christian et al, 1977; Cumper, 1984; Gross, Evans et al., 2001) They may explain roughly 80% of the variation in life expectancy across countries (Cumper, 1984; Gross, 1980). The regression techniques demonstrate associations and can only give some suggestive evidence on the causes of population health. (Millard, 1994; Preston, 1976-1980, 1980; Fulop and Reinke, 1981; Hertz et al., 1994) Recently, in the health area, multi-state multi-disease modelling techniques have been introduced, using existing demographic techniques (WHO, 1995; Weinstein, 1987-1989; Barendregt and Bonneux, 1998; Task Force, 2001).

There is a need to develop the conceptual approaches to make them more explicit and suitable for mathematical implementation at the population level to serve health planners (Feinstein, 1994; Sai and Nassim, 1991). Existing conceptual models and regression results may serve validation purposes when comparing new modelling approaches. This includes both model structures as well as comparisons of outputs. Integrated health modelling attempts are often based on the causal conceptual frameworks mentioned above. Integrated approaches take account of the simultaneous occurrence of multiple risk factors and diseases as well as cause-effect relationships. Feinstein (1994) concludes that these kinds of models cannot be used in the clinical area because of the unique characteristics of each patient, but he concludes that they are appropriate at the population level in support of health policy. Four levels of integration can be distinguished, varying in levels of simplicity. They are described in order of increasing comprehensiveness (Figure 1.1).

**Level 1. Combining population-attributive risks** Walter was among the first to describe the use of the etiological fraction or population-attributive risk (PAR) approach. It makes use of population-attributive risks as defined in epidemiology to calculate the mortality fraction attributable to single particular health determinants at a given moment in time for a particular population. Given risk prevalence figures and the related relative risk of a disease or death, one can compute the risk-attributable fraction and the attributable disease burden. Others applied this approach in a more standardized manner in support of health policy making (Walter, 1976; Sturmans, 1977; USDHS, 1990; Gunning-Scheppers; 1989; Peto et al., 1992; Ruwaard et al. 1993). The approach is relatively simple and does not consider time dimensions nor other epidemiological dynamics. There is, however, a difficulty in combining results for single determinants. These cannot be simply added up since health risks tend to cluster, e.g. in cardiovascular diseases. To account for this, a multiplicative approach has been developed to include the simultaneous occurrence of multiple risk factors (Niessen et al., 1997b).

**Level 2. Multi-state life tables and modelling of disease states** Life table modelling is a standard technique in demography (Chin Long Chiang, 1984; Schoen, 1988) and accounts for the substitution of health risks. Especially for the lower age groups in developing countries and for the higher age groups in all countries, multiple co-existing risks for disease and death are high. If one eliminates a single disease the net health benefit is less than expected due to the other substituting and competing health risks. In a multi-state life table, modelling accounts for at least three states:
Lifetime health

Figure 1.1. Four levels (1-4) of integration and completeness in health approaches. See text below for explanation of numbers.

healthy, diseased and dead (Barendregt and Bonneux, 1998; Nusselder, 1999). It is also applied to developing countries, including future projections (Mosley and Becker 1991b; Dowd and Manton, 1990). More elaborated disease-specific multi-state approaches may still allow for the effects of other diseases (Weinstein, 1987-89; Tsevat et al., 1991; Ruwaard et al. 1993; Niessen et al. 1993; Bonneux et al. 1994). The model techniques have been used to study dependency of disease occurrence by Manton (1982) to estimate morbidity levels (Vaupel et al.,1979) to account for frailty and by Thatcher (1992) to study mortality trends among the very old. This book expands some of the methods used at this level. The topics are described more extensively in chapter 3.

Level 3. Linking national resource allocation and population health For decades health policy makers have been in need of modelling support to improve and document the efficiency of their allocative decision making for the health sector as a whole. Few attempts have been made to implement such an enormous undertaking and none have succeeded. Only few models have been used that link aggregated national resource allocations for health care to potential changes in health status of the
Chapter 1

population (Murray et al., 1996; Patrick and Erikson, 1993; WHO, 1986). The Dutch Central Planning Bureau has been making efforts to implement a comprehensive modelling framework. Sometimes a health economics approach to demand/supply issues is included (Bitran, 1994; Grossman M, 1972; Heller, 1987).

**Level 4. System dynamic modelling** There are only a few system dynamic approaches to health or to health care dynamics (Post and Vennix, 1992; Weishang Qu, 1995). The model described in chapter 3 has been used in combination with a larger dynamic model expanding existing approaches and using elements from these as building blocks (Niessen and Hilderink, 1997).

### 1.3. A TYPOLOGY OF MULTI-STATE MODELLING IN UNCERTAINTY

This section gives a general description of the disease modelling approach and is meant as a guide for the reader for the following chapters. It describes the modelling process and gives examples of the kind of data used as input and of the kinds of outcomes. In the next chapters, multi-state disease modelling will be used to describe changes at the population level in lifetime health effects and medical costs resulting from changes in health determinants.

Multi-state modelling is combining, sometimes overlapping, concepts from epidemiology, demography and health economics. It uses their concepts into one generic mathematical approach that describes population health in a dynamic way. This means that the modelling describes the changing occurrences of diseases in a population. This means that it accounts for how many of the generations alive fall ill, are actually ill, recover or remain ill or die during a defined period in time.

From epidemiology, it uses typical concepts in relation to disease occurrence: prevalence, incidence, mortality, and disease survival, all at a population level (Rose, 2001; Rothman, 1988). Disease prevalence is the proportion of diseased persons in a population and this is the result of the past history of disease occurrence in the involved population. This is particularly relevant when one considers chronic diseases and conditions such as malnutrition or diabetes. The ‘prevalence’ concept is equivalent to the ‘state occupancy’ approach used in demographic multi-state modelling (Mosley and Becker, 1991; Willekens et al, 1982; Murray and Lopez, 1999; Commenges, 1999; Flanders and Kleinbaum, 1995; Hougaard, 1999; Peeters et al., 2002). Recently, the value of the demographic approach for epidemiology has been re-emphasized (Ben-Shlomo and Kubh, 2002). Disease incidence, or the frequency of getting a disease, and disease mortality are two possibilities to enter or leave a prevalence state. The transition from one state to another state is called an event.

Demographic life tables describe a hypothetical cohort of persons going through single or multiple states. It starts at a single point in time, like at birth, and describes the subsequent ageing and dying for men and women, until nobody is alive. Ageing is usually considered in five or one year age groups. Life tables can be age and gender-specific. In the case of multiple states, that describe the survival and death of a cohort, the table is called a multi-state table. When movements back and forth from states are considered, the table is called an increment-decrement table. The input values are usually based on the cross-sectional data for the different population
groups under consideration and hence are based on the living members of all the historical cohorts. This is called a period life table. Life table probabilities may change over time as a function of other variables, like health risks or health care effects.

A so-called dynamic health model describes changes in a population over time for health states, or prevalences, while it includes all existing cohorts under consideration. This means that, while it describes population health through time, the model outcomes at any point in time depend on its state values during all previous time steps. The dynamic elements are twofold. Firstly, there may be multiple health risk states, changing in time due to changing exposure and to selective mortality effects at each age. In time, their increased risk for disease may lead to varying disease incidence. Secondly, there are the states for prevalent disease, possibly multiple ones for a single disease, that are changing due to changing disease incidence, changing disease mortality or moving to other disease state. (Barendregt and Bonneux, 1998) The computed state values for each time step are then the results of many different transitions changing over time. If data are available, one can compute the real life expectancies for each population cohort under consideration. To arrive at an adequate picture of disease occurrence in time all the changes of disease occurrence for each age group, period and cohort need to be known. In that case, a dynamic approach to multi-state modelling would be able to adequately describe disease occurrence in time in terms of resulting disease burden i.e. disease prevalence and mortality. It would allow for calculation of both period and cohort life expectancy for each state, age and sex. In combination with the computed prevalence figures, one can adjust the life expectancy for the duration of disease during the average lifetime, and compute disease-free or healthy life expectancies (Mathers et al, 2001). In practise, disease-specific data in multi-state models are based on mostly single empirical cohort studies of short or long follow-up, like the Framingham study, while general mortality data are based on the cross-sectional statistics for the general population of the period under consideration. The model approach in practice is actually used to supplement the lack of empirical data to describe changes in health, especially in the case of short follow-ups. It may bring together both diverse and conflicting data in a consistent way to describe changing disease epidemiology. Here, computation of initial values for disease prevalence and disease-specific mortality is done assuming equilibrium i.e. without any cohort or period effects (Barendregt and Bonneux, 1998; Niessen et al, 1993).

The multi-state demographic life table can be compared to the Markov modelling approach in health economics (Sonnenberg and Beck, 1993; Commenges, 1999; Russell, 1999; Kuntz and Weinstein, 2001). The common assumption in both methodologies is that the transitions only depend on the characteristics of the preceding state and, possibly one or more co-variants. The transitions between states usually do not depend on the size of the involved states as in contrast with, for example, transmission modelling in infectious diseases. Health economics also uses the concepts of health states and health events. The former can be related to chronic conditions and the latter to acute disease or specific interventions. In addition, it defines two more general characteristics to these parameters: disease utility and
Chapter 1
disease costs (Gold et al, 1996; Kuntz and Weinstein, 2001; Drummond et al, 1997; Johansson, 2001). Disease utility adds a weighting factor to a disease state, indicating the severity of the disease and a particular level of quality of life. When these are known for all ages, one can compute, in various ways, health-related quality-adjusted, hence weighted, healthy life expectancies. When health care utilization and costs are known for the various disease states and for the disease events throughout the history of the disease, one can compute the average disease-specific lifetime costs. Also, in defining time horizons in modelling, health economics may take the lifetime perspective at the population level (Gold et al, 1996; Edwards, 2001). Substitution of health risks may be accounted for and substitution of health care costs may be included like in the demographic life table.

In health economics, computed lifetime multi-state results are also used in relation to optimal allocation or equity issues. The lifetime approach relates to the ‘fair innings’ principle that takes as the objective the same (healthy) life expectancy for the population under consideration (Williams, 1997; Tsuchiya, 2000). In analyses of how to improve population health, it may be important for health policy makers and programme implementers to know the optimal options in the allocation of resources e.g. for primary and secondary preventive interventions as well as curative care options. More general cost-effectiveness analysis aims at the systematic collection of comparable estimates on the population effects and costs of health interventions, including those leading to health risk reductions. (Murray et al, 1999) A health risk assessment estimates an attributive disease burden (Ruwaard et al., 1994). In its extension, a cost-effectiveness approach may deal with the complementary analysis of how this could be done and how the highest health gain per average lifetime can be obtained given the available budget.

To date, analyses of health risks and interventions usually analyse single health effects and single diseases and rarely report the effect of combined risks and interventions. It is known that various health risks may interact and may contribute to multiple diseases. This may be at the same time or later in life. The same is true for health interventions: they may affect multiple diseases. In addition, after reduction of diseases, populations run other disease risks, especially at the higher ages. The multi-state approach allows for assessments of multiple diseases and multiple interventions. Studies that aim to address multiple health risks and multiple interventions need to account for their interdependency, interaction and clustering in relation to disease occurrence both in terms of incidence and prevalence. The multiple population attributive risk approach, like in comparative risk analysis, estimates, in a simplified way, the net and combined contribution of single health risks (Hoogenveen R, 2002; Niessen and Redekop, 2003). Changes in a single health risk or from a single intervention may lead to changes in the attributive disease burden from other health risks. In addition, due to the interaction, the total attributive population effect of the combined occurrence of health risks or interventions on disease prevalence may be different, usually less, than the sum of the single factors.
Accounting for uncertainty

In multi-state modelling, the study of health determinants and disease occurrence throughout a lifetime knows many and large uncertainties. For example, life expectancy at birth in the Netherlands has a standard deviation of about 6-8 years (CBS, 1982). Uncertainties are threefold: in the measurement of input parameter values, in the distribution of parameter values, and in the definition of the model (i.e. equations and values). Epidemiology and demography have a long tradition in presenting uncertainty in measurement and analysis of disease. These analysis methods present uncertainty of results by including standard errors, standard deviations, confidence intervals, or significance levels. Disease modelling in epidemiology and health economics may account for uncertainty through uni-variate or multivariate sensitivity analysis to provide proof of the robustness of the conclusions (Drummond, 1997; Gold et al, 1996). During the past years, the health economics literature has paid considerable attention to the inclusion and presentation of uncertainty in cost-effectiveness estimates (Al, 2001; Russell, 1999; Fenwick et al, 2001; Send and Briggs, 2001; Al, 2001; Walker and Fox-Ruxby, 2001).

This book reports combined applications from the three disciplines to account for these three groups of uncertainties alongside the multi-state modelling. In most presented case studies, input values for the most important input parameters are value distributions instead of their point estimates. These uncertainty ranges can be used to perform sensitivity analyses and to arrive at uncertainty estimates for model outcomes.

The following sections of this chapter describe the conceptualisation steps in the modelling process in general terms, arriving at a generic framework for analyses. The next sections describe model inputs and outputs. These latter sections will provide some illustrative examples of the use of value distributions to demonstrate how uncertainty can be accounted for in the analyses.

1.3.1. FROM CAUSAL FRAMEWORK TO MULTI-STATE MODEL

As in all research, the point of departure in multi-state modelling is a specific research question and not a particular existing (modelling) methodology (Barendregt and Bonneux, 1998). The research question needs to be translated into a relevant causal description of changing occurrence of disease at the population level (Mackenbach, 2001; Kaufman, and Cooper, 1999; Zeeger, 1991). To make this possible, the model approach needs to fulfil two kinds of conditions. Firstly, the disease modelling needs to account in an adequate way, at the population level, for the causal relationships between health determinants and disease occurrence in terms of incidence, prevalence, and mortality of the disease. This can be done by attributing part of disease incidence, survival or mortality to particular health determinants e.g. malnutrition, hypertension, smoking, or health interventions. Secondly, in the evaluation of specific interventions, the model analysis needs not only to describe disease occurrence in epidemiological terms but also account for the specific intervention effects on disease incidence and disease survival, in terms of
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changes in health and costs. This will lead to the inclusion of those health states and transitions that are actually expected to change by the introduction of interventions. The principle of parsimony should be applied: for a simple question one can use a simple model while for complicated questions involving more population health dynamics one needs more complicated modelling.

In the case of multiple risks and interventions, the various risks and intervention options can be analysed individually, and next, in a stepwise manner, added up including more health risks and more interventions, accounting for possible interactions. This qualitative analytic approach is called the design of a causal framework (see an example in Figure 1.2). In broader more comprehensive analysis, one can arrive at an assessment of different risk mixes (or patient profiles) and different intervention packages. Often it is possible, more efficient and simpler to combine the risks, states, or interventions that are not under consideration into one single ‘all other’ category for mortality, morbidity, and health care costs. Often specific data on the heterogeneity of sub-populations are lacking and one will may decide consider only the average disease history for all the various sub-groups combined.

Figure 1.2. Example of a causal framework, illustrating various levels of disease causality (Mathers C et al, 2001).

D=distal determinants; P=proximal determinants; PA=pathophysiological effects; O=health outcomes.

Hence, in the actual modelling process, first, one or more disease states are to be defined. The number of states determines the so-called state space. This is defined by all the various disease states combined, including death. From a population and public health perspective, one will consider all possible, asymptomatic, mild or severe, disease states. In order to describe disease morbidity in general, it may be sufficient to distinguish just a single disease state as in the burden of disease approach (Melse et al, 2000; Murray and Lopez, 1996; Wuerthwein et al., 2001). More extensive evaluations may include multiple disease stages to account for differences in survival (e.g. states after a first and second event, or states with minor and major disability). Usually it is assumed that the states and transitions have no
‘memory’: this means that if one moves from state ‘disease state A’ to ‘disease state B’ the model does not ‘remember’ its state of origin state, state ‘disease A’. This assumption can be altered with either the introduction of separate follow-up states for each original state or by introducing dependencies into the model equations. Last, the approach may distinguish only one or more ‘mortality’ states, which may or may not distinguish death by different causes.

Once the disease space is defined, all disease states are treated in a similar way. Starting with the initial values for each state, computation of all its inflows and outflows, combined for all states gives the population numbers for each of the disease states (i.e. prevalences) for any point in time. After defining the disease states, the transitions, the in- and outflows, are defined. They lead to departure from a present state and entry into another one. These may include dying from the disease or from other diseases, recovery, getting a complication, second event, or exacerbation. Dying due to other mortality causes may be equal or specific for each state. An example of the flows because of the disease process is shown in the Figure 1.2 and is described next (Niessen and Redekop, 2002). Here, one distinguishes distal causes, the macro-determinants, and more proximal causes with (patho-) physiologic effects and outcomes, the micro-determinants. If one would study the effects of more distal causes, the appropriate model would include these determinants and the cause-effect relationships ‘downstream’ in the disease process. Another example would be the case of secondary prevention (see Figure 1.3). Secondary prevention occurs after a first illness episode only. Here, one can start at a more proximal level and one only needs to account for a possible second event amongst those with the disease after a first event. Hence, in this example, one only needs to distinguish one single disease state to compute the potential change in disease re-occurrence i.e. a transition to a state after a second event.

Figure 1.3. shows the causal framework to illustrate how it can be used to evaluate health risks in the case of two diseases and three health risks. It is an example of the generic model approach later discussed in chapter 3 and it distinguishes different levels of causes of ill health. Distal causal factors may be literacy or income status and a more proximal cause may be nutritional status. These lead to more biophysiological changes that ultimately cause ill health. The framework can be used to address the question on the relative benefits of both primary and secondary reduction of causes of ill health.

Applied to the evaluation of cardiovascular risk interventions, one may distinguish multiple risks at the proximal level, e.g. hypertension, smoking, etc (Figure 1.3). These risks may contribute to the occurrence of a variety of diseases like heart disease or stroke (here Disease A and B). Interventions regarding other, more distal, causes, like obesity and socio-economic status, do not necessarily need to be considered when only specific interventions are included. Figure 1.3 illustrates that for a single risk factor intervention it may not always be necessary to identify a disease space that includes all the states for all related diseases. Some of these may be considered together. This is when the explicitly included diseases do not explain a lot of the excess mortality risk. By including a separate risk factor state (here state Risk 1), with an attributive excess mortality, one can compute the remaining attributable disease
burden. In other cases, it might be necessary to do so when the health risk contributes to heterogeneity, i.e. acts as a co-morbid factor and contributes substantially to decreased survival of those having a particular disease. In almost all cases, even for a disease like lung cancer, part of disease incidence will remain non-attributable and unexplained by health risk prevalence. One may be able to ‘explain’ most of the occurrence of infectious diseases, e.g. the incidence of diarrhoea. For most of the chronic diseases this is not possible, although one can attribute them to ‘age’ in general. This still ‘unexplained’ or ‘non-attributable’ incidence can be coined as the natural incidence. In Figure 1.3, this is shown as a double arrow (Murray et al. 2002). Still, including distal causes, ecological, epidemiological and econometric studies of many, poverty-related, diseases may show a correlation with only economic development and not with more specific determinants e.g. in the case of tuberculosis.

Figure 1.3. Example of a multi-state model for prevention based on the conceptual framework in the preceding figure. In all states there is a disease-specific and ‘all other’ mortality risk.

In conclusion, a comparative model analysis of health interventions assesses the potential changes in population health accounting for disease prevalence and changes in disease occurrence. Multi-state and life table modelling techniques can account for ageing, changes in single health risk and combinations of risks, and for the changes in the involved resources for health and health care. The resulting estimates include the interaction and interdependence of health risks and diseases as well as the substitution and competition of diseases and health care costs (Barendregt and Bonneux, 1998; Rothman, 1988; Hoogenveen, 2001).
1.3.2. A MODELLING FRAMEWORK FOR POPULATION HEALTH

This book sets out to describe changing population health under varying external socio-economic and environmental conditions. In the preceding paragraphs it is outlined that population health is seen as determined by a multiple and multi-layered complexity of health determinants. Hence, in order to arrive at an adequate description conceptually and mathematically, it will be necessary to include, in some way or other, all known contributing and confounding factors. This approach assumes that there is a biological potential that unfolds under the influence of favourable conditions. Other factors related to the intrinsic human genetic potential may be relevant, especially in the course of a human lifetime or even across generations. A multi-state approach to a human life course may be useful also to study these effects. (Ben-Shlomo and Kuh, 2002) As their consequences for human health at the population level are only becoming clear for a minority of diseases, genetic factors are excluded.

![Diagram](image)

Figure 1.4. A multi-state modelling framework for population health (Niessen & Hilderink, 1997).

*Figure 1.4* shows an overview of the comprehensive framework that can be used to interpret, describe, and analyse population health. It distinguishes distal and proximal...
Chapter 1

Health determinants, as listed, as a set of state parameters, the disease space, with single or multiple disease states.

Health determinants. In the case of health determinants like health risk factors, two dynamic aspects play a role: health risk prevalence as it evolves over time due to selective survival, and the delayed influences on disease survival. Health risk prevalence evolves over time both as the result of aging and period-related effects such as health interventions. In particular, cohort effects may cause very long term, possibly across generations, dynamic effects. Although subject to the age and period effects, cohort effects may last a remaining lifetime of each generation. Period effects are external and last a short period but may have lifelong effects, like famine or toxic exposure etc.

Disease space with single disease states As said before, multiple disease states allow for a description of population morbidity i.e. people that are ill at a given time period. One may decide not to consider morbidity and include changes in risk factor exposure leading to death only. When one would like to consider morbidity, changes in risk factor exposure will influence disease incidence, with or without a time lag. Disease incidence, in turn, affects disease prevalence and mortality. Disease prevalence becomes a state variable, subject to inflows and outflows and therefore is dynamic in its behaviour. The link between changes in incidence on the one hand, and changes in prevalence and mortality on the other is very direct in the case of 1) highly fatal diseases, like lung cancer or 2) disease with high fatality and with high immediate recovery, such as pneumonia in developing countries. This link is much less direct in the case of non-fatal chronic diseases such as diabetes or COPD. When disease incidence leads to long-term morbidity, the following equations apply (Barendregt and Bonneux, 1999). Then, disease prevalence $p^a_t$, for each age $a$ at time step $t$, is calculated from the previous prevalence level. It starts from an input prevalence level at $t=0$, and increases with the new cases, incidence $i^a_t$, from the population that is without the disease, and as an influx from the preceding age group $a-1$ during the previous time step $t-1$, and decrease with corresponding mortality $m^a_t$:

$$p^a_t = p^a_{t-1} + i^a_{t-1}(1-p^a_{t-1})/1-M^a_{t-1}$$

The computed disease-specific mortality risk is used to calculate changes in population and disease prevalence. Next, an ‘all other’ mortality $M^a_{other}$ risk is calculated for each age group, by subtracting $M^a_0$, the observed total mortality by age, with computed disease-specific mortalities $M^a_d$ for any $d$:

$$M^a_{other} = -\ln(1-M^a_0) - \sum_d M^a_d$$

where $M^a_t$ is total mortality risk and $d$ an index for diseases. With $M^a_{other}$ the ‘all other’ mortality risk and the disease specific mortality risk it is possible to recalculate the total mortality risk for each simulation step $t > 0$.
Disease space with double disease states

The next possibility while in the prevalent disease state (and not dying), is getting another disease, leading to co-morbidity, or double disease states. Striking examples of this trade-off can be observed among the under-fives in developing countries and the aged in developed countries. One may account for the original state for persons already having one disease, defining specific states that register the original state category. In this case, it is possible to account for the increased risk of another disease. One can define the most important co-morbidity states to account for the quantitatively most relevant combinations of diseases. In the next chapters, we selected eight combinations of chronic diseases. The selection is based on the most frequent types of co-morbidity reported in the literature (Ruwaard et al. 1994). In addition, the selection is based on epidemiological arguments. Among the elderly, some diseases may be highly prevalent, as their case fatality ratios are relatively low, like chronic pulmonary disease, heart disease, and stroke (Barendregt and Bonneux, 1998). The last, related, selection criterion is the interdependency of diseases and their relevance for health policy. As death from one disease may be postponed (e.g. from cardiovascular diseases), the nature of the next disease (possibly COPD or cancers) is important for health care demand and the degree of associated disability. Table 1.1 shows some examples of selected co-morbidity states.

<table>
<thead>
<tr>
<th>First disease</th>
<th>Double disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>plus Ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All other cancers</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>plus Lung cancer</td>
</tr>
<tr>
<td></td>
<td>All other cancers</td>
</tr>
<tr>
<td>Stroke</td>
<td>plus Lung cancer</td>
</tr>
<tr>
<td></td>
<td>Other cancers</td>
</tr>
</tbody>
</table>

Table 1.1. Examples of double disease states.

The two building blocks in this generic approach, the health risks and disease space in various combinations, add up to a complex whole. However, in this way, a multi-state model may describe not only homogeneous populations but also account for heterogeneity. It allows for multiple causal pathways from changes in risk factor prevalence through the intermediate diseases to risk-specific changes in total mortality and population life expectancy. Mortality selection follows from the effect that people at risk run higher risks to die, and are therefore selectively removed from the population. Mortality selection may decrease for example among malnourished under-fives, when they receive vaccinations or treatment for single diseases like malaria. The prevalence of malnutrition in this case will go up. As this group runs much higher risks for other disease like diarrhoea or pneumonia, population mortality for these diseases will go up more than proportionally. Therefore, the net population benefit of the interventions will be much less than expected.
While these effects certainly exist, it is still uncertain whether they are quantitatively important enough to reward the additional model complexity. Our calculations including malnutrition (in the next chapters) amongst under-fives in relation to infectious diseases showed indeed an effect of mortality selection. The dependent competing mortality risk turned out to be small compared to the independent competing risks (or substitution of causes of death). The effect of mortality selection is also demonstrated in the chapters on diabetes mellitus. There, the probabilistic multi-state model, by its nature, cannot ignore mortality selection, through selection by complication. When one complication or cause of death is reduced (e.g. end-stage renal disease), figures for both preceding complication stages (e.g. neuropathy and retinopathy conditions) go up because of increased survival. In comparison, the results from the models that do not allow for mortality selection may differ significantly only under extreme assumptions for some groups. Amongst the very young and old, mortality risks can be extreme but in other cases not. Nevertheless, the phenomenon should be kept in mind during the definition of the causal framework, as it might be important in relation to the research question.

We have seen that the selection and definition of health risks and disease states simultaneously determine the in- and outflows between the states. These flows/transitions can be modified to include the effect of health interventions. Primary preventive interventions may inhibit people to run health risks while secondary prevention may stop or postpone people from falling ill again or get worse. Curative interventions may lead to cure with or without returning to the preceding risk state. They also may lead to only partial recovery, less disability or prevention of more severe diseases.

Selection of health risks and health interventions

The overall level of the main health determinants represents those health determinants that the population is exposed to and these determine the rate of death. These main factors (Figure 1.4) may be food consumption, access to clean water, exposure to parasites and others, and there are life-style-related factors, like smoking and high blood pressure. The presence of specific health care interventions may change survival in disease states and the transitions between stages.

Given a particular research question, the inclusion criteria for specific risks and interventions are, mainly, the availability of empirical evidence of a quantifiable relation with the occurrence of disease(s) and their influence on mortality and morbidity levels (Schofield et al., 1991; Walle van de et al., 1992; Winkelstein, 1993). Equally important is the availability of epidemiological and statistical data at a population level. In our generic approach in the next chapters, we selected a maximum of 12 exposure categories and modified only those transitions that have been proven to change due to effective interventions. These are in general transitions related to mortality and not to severity. In the approach, occurrence and clustering of multiple exposures within population sub-groups are taken into account. This results in a clustering of higher absolute risks of one particular disease as well as higher competing risks of other diseases, especially among children and the aged. Intervention effects might be higher or lower in these subgroups, depending on the effectiveness evidence. Recording of both the original determinant category
of the incident cases as well as the origin of those already prevalent with disease makes it possible to attribute disease and death to specific health risks.

The general modelling principle is that one takes into account only those risks or interventions under consideration i.e. the principle of parsimony. All other factors, components of the population health framework, can be lumped together. One can include all of them in one single ‘other’ category for each parameter. This may be one single ‘other risks’ category, ‘other mortality’, or ‘other morbidity’ category or ‘other’ health costs category. The health determinants discussed can be operationalised as follows:

- Economic development, as the main socio-economic distal determinant of health. Usually, in an operationalisation, one uses gross national product per capita (GNP) as expressed in US-dollars, compared to a reference year, possibly recalculated, corrected for purchasing power parity.
- Female literacy level. This is expressed as the fraction of the adult female population that is literate. This depends very much on the development in gross national product but with a 20-year delay (Vianen et al. 1995).
- Nutritional health determinants. This is usually operationalised as food availability (food per capita), expressed in kilocalories intake, and taken as an approximation of nutritional status. Here distribution issues play a distinct role.
- Drinking water and sanitation, as the main environmental determinant. This can be defined as the fraction of the population with proper access to safe drinking water and having sanitation. In addition, water handling is an important factor in relation to water-borne diseases. In the case of large discrepancies between the two parameters, safe drinking water coverage can be chosen. This factor is the more determining of the two (Esrey, 1985 & 1991).
- Numerous proximal determinants. Epidemiology has identified a large number of proximal determinants, i.e. health factors that influence the risk of getting a disease or survival after getting a disease. The most important are tobacco use, high blood pressure, and hypercholesterolemia.
- Numerous specific health interventions. Both clinical epidemiology and health economics have produced a great deal of literature on the health effects and costs of specific interventions, usually in well-defined patient sub-groups.

### 1.3.3. MODEL INPUTS: VALUE DISTRIBUTIONS FOR STATES & FLOWS

Once a model structure has been defined, the model has to be filled and its outcomes specified. The next two sections describe the general approach to the computation of input. It will focus on how value distributions are accounted for as these are a source to account for uncertainty.

Model inputs can be divided into those related to health risks and those related to the disease space. Both groups may use one year age groups or, more commonly, 5-year age groups like 0-4, 5-9, up to 95-99, 100-plus. For a disease with different levels of severity, there is an option to include costs as disease specific costs per
incidence case, per event (such as a recurrent attack or relapse) or per prevalent severity class, by 5-year age groups and sex. The kinds of additional population data that are used depend on the model approach to the diseases. They may consist of 1) total mortality rates, by age and sex, 2) population numbers, by age and sex and, 3) birth rates by age of mother. For disease or risk prevalence and event probabilities, disease disability weights can be added i.e. the mean or point estimates of the disability weight for the disease state, by n-year age group and sex. The involved medical costs of diseases are to be defined next i.e. as medical costs per disease stage or event, by age group and sex. Health risk with continuous distributions (instead of categories) gives more accurate estimates of changes than dichotomous categories as they can account for distribution shifts and shapes. Changes in disease processes at times can be more adequately modelled by including more prevalence stages e.g. mild and severe (as with stroke) or including early and late complications (like for diabetes mellitus). In case a disease model keeps account of the original health determinant categories, it allows for an estimation of risk-attributable morbidity and mortality.

For each risk or disease, intervention options can be defined, as well as their mode of effectiveness and the medical costs involved per disease stage, by age group and sex, as necessary. This again can be as point estimates or based on uncertainty distribution.

**Input data: population-attributive risks**

Health risk data can be differentiated into 1) data for the description of prevalence of health risks over time and 2) data describing the links with disease in a comparative risk assessment. Risk prevalence data usually account for age effects in exposure. Relative risks are usually by five-year age groups, sex and exposure category. Once combined these data account for the risk-attributable fraction of disease incidence, or, but less, of survival. Multiplicative population attributable risks in relation to disease incidence and medical cost are described in more detail as these are rather uncommonly used in epidemiology and health economics.

The multiple health determinant approach frequently requires a total population-attributable risk (TPAR) for each disease under consideration. The population-attributable risk is the calculation of the fraction of incidence or mortality that can be attributed to a single exclusive health risk factor R as compared to one single reference risk level (USDHHS, 1990; Ruwaard et al., 1994; Niessen et al., 1995; Rothman, 1988; Hoogenveen, 2001):

\[
P_{AR_R} = \frac{P_R \times (m_1 - m_0)}{1 + P_I \times (m_1 - m_0)}
\]

(1)

with \(P_R\) the fraction with high risk level, \(m_0\) the incidence or mortality for the referent mortality risk level, \(m_1\) the mortality risk for the high risk level, and \(P_I\) is the fraction with the risk. When we introduce relative risks, we can rewrite the formula (see also Figure 1.2):

\[
P_{AR_R} = \frac{P_R \times (RR_R - 1)}{1 + P_I \times (RR_R - 1)}
\]
Or for multiple, stratified, risk factor classes:

\[
\text{PAR}_R = \left\{ \sum_r P_r (\text{RR}_r - 1) \right\} / \left\{ 1 + \sum_r P_r (\text{RR}_r - 1) \right\}
\]  

(2)

Here \( \text{RR}_r = m_1 / m_0 \) based on class \( r \)-specific excess mortality. Here, it is assumed that the sub-populations for the two risk levels are comparable with respect to all other risk factors. In this case, we can use the relative risk that is marginal with respect to the other risk factors. If not, this needs to be corrected for (Rothman, 1998; Hoogenveen, 2001; Holman and Armstrong, 1992). Risk factors with a relative risk larger than 16 may explain over a 75% of disease incidence. Smoking has relative risks \( > 20 \) for lung cancer and explains more than 95% of its occurrence. In the case of continuous variables (e.g. cholesterol level or blood pressures) the PAR formula is similar:

\[
\text{PAR}_R = \left\{ \int_{r \geq t} (\text{RR}(r)-1) f(r) \, dr \right\} / \left\{ 1 + \int_{r \geq t} (\text{RR}(r)-1) f(r) \, dr \right\}
\]  

(3)

Here, \( r \) is the index for the risk factor \( R \) categories as \( \text{RR} \) is based on the continuous function of \( r, f(r) \). The \( t \) is the chosen cut-off point to define the increased risk levels. The function \( f(r) \) is the probability density function for risk factor \( R \). All values can be age and sex-specific. Next, considering \( f(r) \) for those RR's \( > 1 \):

\[
= \int_{r \geq t} f(r|E=1) (\text{RR}(r)-1) / \text{RR}(r) \, dr
\]

(4)

Here \( f(r|E=1) \) is for the relevant prevalence fractions for class \( r \) for the cases. This approach makes it possible to account for shifts in the prevalence distribution over risk factor classes, as is used in the comparative risk approach (cf. Figure 1.5) (Niessen et al. 1995) In the case of multiple risk factors with an equal number of sub-populations, the approach needs adaptation. When these two sub-populations are not comparable with respect to some other risk factor \( S \), due to clustering or confounding risks, the population-attributable risk formula becomes more complex. (Walter, 1976-1983; Walker, 1981; Rothman, 1988) The imputed risks need to be corrected for confounding, first. The PAR for risk factor \( R \) is expressed as a function of conditional mortality risks (given the reference risk and given \( S \)) and conditional risk prevalences:

\[
\text{PAR}_R = \left\{ \frac{P_{R0} \ast (m_{R0} - m_{00}) + P_{RS} \ast (m_{RS} - m_{Sj})}{\Sigma_{ij} P_{ij} \ast (m_{ij})} \right\}
\]  

(5)

\( P_{ij} \) is the joint probability distribution for \( R \) and \( S \) together and \( m_{ij} \) the incidence or mortality risk for risk factor \( R \) level \( i \) and \( S \) level \( j \). When we again introduce relative risks and assume that (1) the conditional, corrected relative risks are independent of
the other risk level, and (2) the combined relative risk is the product of the conditional relative risk, we find:

\[
PAR_R = \frac{P_R \times (RR_R(S) - 1)}{P_{00} + RR_R(S) \times P_{00} + RR_S(R) \times P_{0S} + RR_R(S) \times RR_S(R) \times P_{RS}}
\]

(6)

Here \(P_R\) is the marginal fraction with high risk level R level, \(RR_R(S)\) the (corrected) risk factor R relative risk conditional on the level of risk factor S.

The multiplication of PARs’ complements computes the joint PAR complement: \((1 - PAR_{RS}) = (1 - PAR_R)(1 - PAR_S)\) or \(PAR_{RS} = PAR_R + PAR_S - PAR_R PAR_S\). This is possible in the case of multiplicative risks \((RR_{RS} = RR_{R0} RR_{0S})\) and independently distributed risk factors \((P_{RS} = P_R P_S)\). As most risks are multiplicative and not additive, this approach is appropriate. The net effect of a single risk factor in all calculations depends on the presence of other risk factors (one or more). In addition, in the case of attributing reductions of risk factors in a population, the net effect will depend on the arbitrary order in which factors are reduced. One solution is the calculation of the average PAR, given all possible orders of risk factor elimination. This can be called the ‘average attributable fraction’ (Eide and Gefeller, 1995). In the integrated modelling approach used in this book, included in cost-effectiveness analyses, all options can be evaluated. We need to make one assumption to describe single population-attributable risks in the case of confounding risk factors and one assumption to describe total population-attributable risks. The first one relates to the joint risk factor probability distribution, the other relates to the combined effect of the risk factors. These assumptions are dependent. Usually one can assume a multiplicative model with independently distributed risk factors. Then:

\[
TPAR_{RS} = 1 - (1 - PAR_R) \times (1 - PAR_S)
\]

(7)

Here \(TPAR_{RS}\) is the total proportion of disease that can be attributed to the risk factors R and S. Both \(PAR_R\) and \(PAR_S\) are the population-attributable risks according to formula (1). Taking into account clustering of the risk factors but still a multiplicative relative risk model, the total population-attributable risk can be written as:

\[
TPAR_{RS} = 1 - (1 - PAR_R)(1 - PAR_S) C
\]

(8)

with:

\[
PAR_R = \frac{P_{1} \times (RR_R(S) - 1)}{1 + P_{1} \times (RR_R(S) - 1)}
\]

(9)

C is an observed correction factor. The C usually will be < 1, since clustering diminishes the population effect of two health determinants. Note the similarities and differences between the corrected population-attributed risk \(PAR_R\) in formula (8) and the original population-attributive risk \(PAR_R\) in formula (1). The values for the PAR for single risks and a combination of risks can vary considerably, especially
at the lower range of prevalence values. The correction factor \( C \) is determined by the clustering factor, the conditional relative risk and the separate population-attributive risks. One can show that the two effects of positive or negative clustering on the total population-attributive risks are opposite: the combined relative risk is smaller than the product of the marginal relative risks, and the joint probability of two high (or low) risk factor levels is greater than the product of the marginal high (or low) risks. Therefore, the effect of clustering on the total population-attributive risk is expected to be small, compared to the result of formula (6). An example is given in the next figure.

**Example input data PAR distribution.** Figure 1.5 gives an example of a PAR distribution for ischemic heart disease. This distribution is based on 1) the continuous, normal distributions for blood pressure in the Dutch population, defined by a mean and a standard deviation and 2) a continuous relative risk function for blood pressure and cholesterol. (Niessen and Redekop, 2002). The average value for women, age 30-44, is 0.10 and for age 60-69 it is 0.36. The value distributions show that at the younger ages the contribution is skewed to the lower proportions: the effect is determined mainly by a large number of low risk cases. The distributions at the higher ages shows an even distribution determined by both equal numbers of low and high-risk cases. The figure leaves the debate on preventive approaches aiming at
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the population or/and high-risk groups unresolved (Rose, 2001; Murray et al., 2002; Niessen and Redekop, 2003).

**Input data: utility values for disease states**

General health outcome measures at the population level combine time spend with disability from different diseases into a single outcome. To be able to add up times spend with each disease, one uses severity weighting of the different diseases and/or different disease stages under consideration. For this purpose, clinimetrics and health economics have developed a family of weighing methods to account for disease severity. Once severity classes are distinguished, a utility weight can be added to each of them to facilitate comparisons across diseases and disease stages. There are several ways to arrive at a value. A broad distinction is made for value weights given by the public, generally healthy persons, and value weights given by patients i.e. the public or patient utility values. Values in general range between 0 (death) and 1 (completely healthy). Sometimes conditions are considered worse than death and receive a negative value (see Figure 1.6). As values differ among individuals, depending on coping, culture, and other background characteristics, one may consider including the distributions of these values in a comparison of the conditions with and without the intervention.

![Figure 1.6. Distributions of utility values for major stroke by respondent group.](image)

**Example input data: utility distribution** Figure 1.6. shows the distribution of utility values for major stroke among patients at risk for stroke and in the general public. The former is based on patient interviews and the latter on EuroQol scores (chapter 6). One can see that in this case a subgroup of patients at risk has very different values than the public. Some of the outcomes in chapter 6 would be very different using these utility weights. Hence, research outcomes will be different depending on whose values are counted. Very often one does not find these large differences
between patient and public values. Patients with a condition tend to cope and rate their health themselves somewhat higher than the healthy public tends to do.

**Input data: effectiveness of interventions**

In general, uncertainty distributions of intervention effects are included based on the mean and standard deviation from the relevant empirical study. The usual assumption is that this is a normal distribution.

**Example input data: effectiveness distribution.** Figure 1.7 gives the case of the population level of diabetes control as an example of effectiveness distributions that are non-normal. It shows the level of diabetes control as measured by the percentage of glycosated haemoglobin (HbA1c) blood values as it is in the Netherlands at the moment. In addition, it shows how much it can be improved by the implementation of guidelines (chapter 8). The blood values are skewed towards the normal, lower level i.e. 6.0%.

![Figure 1.7. Patient population distribution of HbA1c values during current (---) and experimental guideline care (-- - -) (Niessen and Casparie, 2001; chapter 8).](image)

**Input data: disease measures**

Disease input data may vary, depending on its definition as simple a cause of death, or as a cause of morbidity as well. In the latter case, there may or may not be additional input of disability weights (see above) and disease costs. The minimum data requirements for each disease are 1) disease specific mortality rates, by n-year age groups and sex, 2) disease specific incidence rates, by n-year age groups and sex and, 3) disease specific prevalence rates at t=0, by n-year age groups and sex. This incidence/prevalence/mortality (IPM) approach gives an elementary description of disease occurrence in the population (Barendregt & Bonneux, 1998). The approach is based on a single disease stage for each age and sex for each year of the disease. Hence, the description of the disease history is also based on this. Other more
elaborated research questions may need more stages and a different approach to account for the disease history like in cancer.

If one would like to study changes over time as a consequence of changes in determinants and diseases parameters (IPM), the minimum additional input would be trend values for these input parameters (Niessen et al., 1993). Other, more extended approaches would include changes in health risks or services effects.

**Example input data: trend uncertainties.** Figure 1.8 shows the ranges in epidemiological trends for the changes in incidence and survival that are consistent with the trend in disease-specific mortality (chapter 5). As can be read from the x-axis, the incidence trend ranges from -1.7% to -2.1%.

![Graph showing incidence and case-fatality trends for stroke.](image)

Figure 1.8. Example of uncertainty ranges for input values: incidence and case-fatality trends for stroke. The mortality line is the isoquant. The lines indicate values ranges found in the literature. The bold line indicates the input uncertainty range for the trends (Niessen et al., 1993; chapter 5).

### 1.3.4 MODEL OUTCOMES: LIFETIME HEALTH & MEDICAL COSTS

Computation of population health indicators and cost of medical care is in general straightforward as these are based on prevailing epidemiological, demographic and health economics concepts. The output as a rule either shows both the reference and the intervention scenarios, or the difference between the two.
1.3.4.1. CHANGING HEALTH

Output data: weighted life expectancies
In the demographic literature general population health measures are described (Matters et al., 2001). When disability weights are defined, several output items appear with ‘disability’ in the name: ‘years lived with disability’, ‘disability adjusted life expectancy’, etc. On the disease specific level the ‘disability rate’ is calculated by multiplying the disease prevalence with the disability weight. These disability rates can be multiplied with the population to yield ‘years lived with disability’ for that particular disease. When the disability output is on the level of the population we need, similarly to mortality and costs, an ‘all other’ disability rate to calculate total disability. With the ‘all other’ disability rate and the disease specific disability rates the total disability rate for each simulation year is calculated. This total disability rate is used to calculate, for each time step, the disability adjusted life expectancy (DALE) using the following equation (Barendregt & Bonneux, 1998):

\[ DALE_a = \sum_{i=a}^{100} L_i^a (1 - W_i^a) \]

Here \( L_i^a \) is the number of years lived by the average person of age \( a \) between time \( t \) and \( t+1 \). \( W_i^a \) is the average disability weight by age and time, and \( L_i^a \) the number of persons under consideration. The disease burden at the population level can be expressed in various other comprehensive health measures. Total years lived with disability on the population level are calculated by multiplying with population numbers. One more known measure needs to be distinguished here: the loss of disability-adjusted life years (DALYs). (World Bank, 1993) In this approach time spend with disease, as an incident and prevalent case, are added to the time lost due to premature death as compared with the golden standard life table ‘North’ (Murray and Lopez, 1996; Garcia-Rodriguez and Cayolla da Motta, 1989). In the multi-state approach, the duration of an incident period depends on the disease: in general two weeks for infectious diseases and one month for chronic diseases. Prevalence cases are counted as lasting for the whole year. The time spent with disease is weighted by degree of related disability. The distribution of the severity of disability has been estimated for incident as well as prevalent cases by a Delphi-panel of experts (Murray, 1996). Figure 1.6. showed uncertainty in utility values.

Example output data: DALE loss by cause. Figure 1.9 shows the DALE and the DALE years lost by cause in an estimation of long-term net contribution of health determinants to the population disease burden for The Netherlands. The generic framework is used to relate the historical and projected health risks prevalences for all macro- and micro-determinants to the changes in disease and mortality. All possible multiple risk combinations are considered simultaneously. Given these
1.3.4.2. CHANGING MEDICAL COSTS

**Outcome data: risk-attributable medical costs**

The estimated disease occurrence data can be related to direct medical costs or indirect societal costs e.g. sickness benefits for the employed population. Medical costs at the disease specific level can be per incident case, more general per event, for acute care, or per prevalent case, for chronic care. Next, for each disease the costs per capita in the population can be calculated in a cross-sectional way by multiplying the disease prevalence with the cost per case or, longitudinally across a lifetime i.e. for each cohort. These costs per capita or lifetime can be multiplied with the absolute population figures to estimate total costs by disease.

**Example output data: attributable costs.** Table 1.2 gives an example of attributable prevalence fractions to compute the total costs of diabetes mellitus in the Dutch population. (van Os et al. 2000). Given the total costs for each disease category one can compute the fraction of total costs attributable to diabetes. For the Netherlands
medical costs are estimated at 1.67 billion Dfl1994 (1.55-1.87 billion) and the indirect costs at 0.2 billion Dfl1994.

<table>
<thead>
<tr>
<th>Diabetes-related disease</th>
<th>Population-attributable fraction (men/women)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age group</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.20/0.25</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>0.12/0.03</td>
</tr>
<tr>
<td>Eye disease</td>
<td>0.11/0.14</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>0.11/0.11</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.24/0.22</td>
</tr>
<tr>
<td>Cellulitis of leg or foot</td>
<td>0.02/0.02</td>
</tr>
<tr>
<td>Chronic ulcers</td>
<td>0.19/0.24</td>
</tr>
</tbody>
</table>

Table 1.2. Population-attributive fraction for the costs of diabetes complications, by age, sex, and by diabetes-related disease based on prevalence figures and relative risks for the related diseases. (Osvan et al. 2000; chapter 8).

*Example output data: lifetime costs.* On the next page *Figure 1.10* shows the lifetime costs of stroke by age of onset, gender and severity. A multi-variate sensitivity analysis has shown that the chance of admission to a chronic care institution is the single most important factor. The lines above and below both lines for major stroke in the figure indicate the results of the sensitivity analysis. They show the 95% confidence interval of the estimated lifetime costs as a function of the probability distribution of admission.

![Figure 1.10](image)  
*Figure 1.10. Lifetime costs (Dfl1996) of stroke by age of onset, gender and severity. The thin lines for major stroke indicate the upper and lower estimates based on uncertainty ranges for input values (Niessen et al. 2000; chapter 6).*
1.3.4.3. CHANGING HEALTH AND COSTS: COST-EFFECTIVENESS

Outcome data: cost-effectiveness ratios
Uncertainty ranges in the input values will yield uncertainty ranges in outcome parameters regarding health outcome and health care costs. General aggregate outcomes are life years lived or life-years gained and total or additional medical costs spent, defined by a mean and standard deviation. The combined outcome measure is the medical costs per life year gained as compared to a non-intervention situation i.e. the incremental cost-effectiveness ratio (CER) for the intervention. Including uncertainties in this outcome measure has become rather common in the past years in economic evaluation. Some may argue, however, that adding uncertainty to outcomes is only necessary if this is of use for future studies (Claxton, 1999). Al has given an introduction to uncertainties issues (Al, 2001). First we give an example of how uncertainty is dealt with in the case of one intervention for various population groups. Next, we give an example for multiple interventions and multiple groups.

Example output data: cost-effectiveness acceptability curves Figure 1.11 shows the example of acceptability curves for one intervention option as a way to present the uncertainty ranges for cost-effectiveness ratios. An acceptability curve allows policy makers, given a particular acceptable budget level (x-axis) to chose the intervention population and identify the level of uncertainty (y-axis). In a Monte Carlo simulation the probability for each possible cost-effectiveness ratio, i.e. effects divided by costs, is computed using random draws from the output distributions (mean and standard deviation) for health benefits and for the related medical costs. This in turn gives an outcome distribution for the CER. The figure gives the cumulative probability for each value of cost-effectiveness ratio or lower by sex and age of onset. Depending on the level of CER that is acceptable and the corresponding likelihood of this CER, policy makers can select an intervention option.

Figure 1.11. Cumulative outcome distributions for cost-effectiveness: the acceptability curve for stroke units for men (M) and women (F) by age of onset. (Niessen et al., 2000; chapter 6).
Example output data: stochastic league table. When there are many intervention options, it is difficult to combine them all in a single acceptability curve. Still, one can compute the probability of including (a combination of) options in an optimum choice, given a particular budget level. Figure 1.12 shows an example of a stochastic league table for eight, mutually exclusive intervention options and their combinations for the patient group with diabetes mellitus type 2 in secondary care. At each budget level, it shows the likelihood for an option to be the optimum choice. In a Monte Carlo procedure, the outcome distributions for health benefits and for medical costs for each intervention mix are used to choose the most likely most cost-effective option, given the available budget level. As the budget increases, more expensive options can be included. Again, like in the acceptability curve, it allows policy makers to make choices given the available total budget level (x-axis) and to identify the most likely (y-axis) optimal intervention mixes for this patient group (Baltussen, 2001). One can see, as an example, that at low budget levels (A in Figure) the option S2.GC are most likely (≈100%) to be the optimum choice. At higher budget levels of Euro 12,000 available per lifetime, S1.GC and S1.GC+S2.GC (B in Figure 1.12) are equally likely to be a good choice.

Figure 1.12. Example of stochastic league table: probability of inclusion (y-axis; %) in an optimum package by available lifetime budget (x-axis; 1996€) for intervention mixes for secondary care patients (S) (Baltussen et al., 2002; chapter 8).

‘1’=preventive diabetes control; ‘2’=preventive care of late complications; ‘CC’=current care; ‘GC’=guideline care.
1.4. GENERAL RESEARCH QUESTIONS AND BOOK OUTLINE

This book addresses the health policy questions 1) what factors determine population health and 2) how can it be improved. International and national policy needs require comparative analyses to answer important general questions like: What are effective and efficient ways to improve health and what are effective and efficient programme interventions to reduce diseases and mortality at the population level? What are the changes in population health and health costs because of single or combinations of interventions? Which health care packages are likely to be the optimal choice in the allocation of health resources? How can population health be maximised and which population groups need to be treated to yield most benefit?

An analytic approach addressing these questions needs to consider the main input-output relationships between population health and both environmental and societal resources. The integrated multi-state modelling approach seems to qualify for this and will be tested to explore and define policy questions and examine specific hypotheses in epidemiology, health economics, demography, and public health.

The research starts with the postulate that the changes in population health under the influence of health determinants can be analysed more adequately in a dynamic, disease-specific way, accounting for the level of health determinants. This means that it is based on epidemiological principles and includes concepts like incidence, prevalence and survival, including the empirically documented effects of health determinants, in particular risk factors and health care interventions.

The second research postulate is that some ‘roads to health’ lead to health more quickly and at the expense of fewer resources than other roads. There are many diseases and many intervention options. There are many ways to fall ill, many causes to die from and a diversity of instances to actively intervene. Hence there are many options to prevent people from falling ill, to improve recovery and quality of survival after falling ill and to avert premature mortality. Hence, there is certainly no one single way to promote population health best. Given the scarcity of resources and increase in demand for them in the world's populations, there are many needs for methods to describe the interactions better and find more optimal pathways to maintain and increase health levels. This book explores usefulness of the multi-state method for these purposes.

This book continues in the next chapter to describe the dynamic epidemiologic occurrence of disease in populations and gives an overview of the major known health determinants, health risk factors and health care interventions. The chapter gives an overview of how it is understood that, during the past century, most populations of the world have experienced increases in their levels of social welfare and economic development and entered the health transition. The third chapter specifies further a generic framework for multi-state population health modelling to describe the dynamics of disease occurrence and related health care costs in populations and links this process with the major known health determinants: health risk factors and health care interventions. In the fourth chapter the multi-state approach has been tested for
three countries, making use of single states for multiple diseases simultaneously, to
describe in an aggregate way changes from high to low mortality. Next, the method
has been applied for single diseases, and addresses more specific research questions.
Interventions that are more specific require multiple disease states. Case studies are
for the old-age diseases stroke and diabetes mellitus type 2. The stroke model
includes states that account for the remaining severity and the duration of the
disease. The diabetes models include states that account for the severity of long-term
complications during the course of the disease. The last two chapters discuss the use
health policy makes of the results of the type of research presented and present the
general findings, the controversies and recommendations for future research.
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SECTION II

THE DYNAMICS OF DISEASE OCCURRENCE
HEALTH TRANSITIONS: HEALTH DETERMINANTS AND DISEASE OCCURRENCE

2.1. SUMMARY

Introduction The second chapter justifies the selection of the research theme and chosen modelling approach. It gives an outline of the current health issues in various world regions using concepts from the health transition theory and epidemiological understanding of disease occurrence.

Methods A review of the health transition literature.

Results It gives an overview how most populations of the world during the past two centuries experienced increases in social welfare and economic development and entered the health transition. The result has been an increase in life expectancy and an increase in size and ageing of the world’s populations with an unprecedented demand for societal resources. In consequence, all over the world, societies are confronted with a huge demand also for health resources due to increased survival and the ageing process. The investments during the later stages of life need to be greater as they show diminishing returns. In contrast, in the poorer regions of the world, population increases have caused a pressing need for continuing investments to just maintain present health standards. The awareness has grown that the natural assets relevant to human health, especially food and water, are scarce and diminishing. At the same time, there is hope. The past decades have shown that, at relatively low budgets per capita, modern insights in prevention and treatment have a lot to offer to the poorer nations.

Conclusion The description of the patterns of changing population health leads to the postulate that in an analytic approach to population health issues one has to account for multiple roads towards health i.e. multiple health determinants, diseases and interventions, within each stage of the health transition. In addition, the approach has to account for both morbidity and mortality as the important outcomes. Multi-state modelling of population health and resource use seems to be a methodology that can incorporate these aspects. This is the core theme of this book.
Chapter 2
In the coming section we give a justification of our approach and summarize the population and health issues that we address. We first outline the theory on the health transition and then we give an overview of the various health problems during the health transition stages. Last, it leads to the postulate that multiple roads to health are possible, both at an aggregate level of general population health and at a disease specific level. It leads to the conclusion that multi-state modelling might be a suitable analytic approach.

During the past century, most world populations have experienced an increase in their levels of social welfare and economic development. These changes have shown a concomitant increase in the average life expectancy at birth and a decrease, although slower, in fertility levels (World Bank, 1993; UNFPA, 1995). The result has been an increase in worldwide population size and a demand for resources unprecedented in history (WCED, 1987; UN, 1992). Reduction of health risks and increased access to health services have resulted in a worldwide average life expectancy of more than 65 years with a simultaneous increase in population size. Although the fertility rates are dropping, for some countries even rapidly, the global population is still growing with 1.5% per year. Presently, world population size in the year 2050 is estimated to be determined for about 50% merely by the present size of the fertile female population. The remaining 50% is thought to be determined for one third by the continuing increase in life expectancy and for two third by fertility levels beyond replacement level (Bulatao, 1989). In addition, ageing societies across the world are confronted with an excess demand for health resources due to the ageing process itself. Investments in health provision in a later stage of life need to be greater as they show diminishing returns (Kane, 1990). In contrast, in the poorer world regions, population increases have caused a pressing need for continuing investments to just maintain health standards (Evans et al., 1981; World Bank, 1993).

The awareness has grown that in these regions the environmental assets relevant to human health, especially food and water, are scarce and diminishing (WCED, 1987). The theory that addresses changes in population size and health in one general frame of reference is that of the health transition (Caldwell et al., 1986; Caselli, 1991, 2002; Bobadilla et al. 1993; Murray et al. 1994; Ness, 1993; Pollard, 1990; Possas, 1995). The health transition is defined as including all these changes as well as the concomitant changes in the organization of social and health-related services (Frenk et al. 1994). Its theory describes how populations may go through typical demographic and health stages (Figure 2.1) when they change from living in pre-industrial conditions to those of post-modern societies (Omran, 1971). High fertility levels and a low life expectancy with an epidemiological pattern of infectious diseases characterize the early stages. In the last recognized stages low levels of fertility are dominant sometimes even below replacement level, life expectancy is high and diseases are postponed until the last years of life. The changes in fertility and mortality often have a different timing. Also specific sub-populations may find themselves in varying stages of these two processes (Robinson, 1992 on Kenya or Bobadilla, 1993 on Mexico). The basic idea of this theory is that in general there is a convergence of developmental directions, with some exceptions (Caselli, 2002).
can be concluded that, on an aggregated level and on a long-term basis, convergence is often the case and can be generalized somehow for at least the various world regions. In case of more specific research or policy questions that are related to a particular period, situation and population, one has to account for particularities and exceptions.

Figure 2.1. The three stages within the health transition. The left y-axis ( ) shows the change in life expectancy and the right y-axis ( ) the change in fertility. Bold numbers are the three transition stages (see 2.3).

2.3. POPULATION HEALTH ISSUES BY TRANSITION STAGE

Unbalanced socio-economic development and unbalanced investments in social and medical services during the past five decades have lead to the characteristic population and health issues as we outline them (WCED, 1987; World Bank, 1993). They are all related to access and distribution of resources. They can be categorized by their relationship with the three stages of the health transition (Figure 2.1). They are: a first stage of high mortality in the early phases of the health transition, an intermediate stage with declining mortality and health deficits among populations in the midst of the transition with a growth in population size and more competition for resources, and a last stage with low mortality and associated health needs of aged populations in a presumably new steady state with a near zero, or even a negative population growth, with fertility controlled and survival improving even more. We summarize the stages in the next sections.

2.3.1. HIGH MORTALITY STAGE

As said, in almost all countries of the world, mortality and fertility rates are dropping, often fast. Still, there are huge unmet needs for broad and more specific
health transitions as concluded by the international agencies (UNDP, 1995: UNFPA, 1995: UNICEF; 1995). Accumulated mortality risks throughout the fertile period still might be ranging from 1 out of 40 in South Asia to 1 out of 20 in Africa (Graham, 1995) and their contribution to the total health burden is large (Figure 2.2). Conditions related to reproduction are mostly preventable and/or curable. Policies that are proposed vary from broader socio-economic interventions such as education and labor to more health service orientated investments related to maternal health and family planning (UNDP, 1995; Hutter et al., 1995). Countries in this stage show many disparities in general health also (Pannenberg 1978; Mosley and Cowley, 1991; World Bank 1993). Agreement seems to be growing that both socio-economic inputs and essential preventive and curative health interventions can contribute to health levels (McKeown, 1976; Preston, 1980; Murray, 1994; Phillips and Verhasselt, 1994). A major complication is that health determinants can be substituting, complementary and synergetic (King, 1990; Niessen and Hilderink, 1997). The effects of single disease interventions tend to be tempered considerably because of this. Preventable and curable diseases form a major part of global total burden of diseases and amount to about 25 million deaths annually (Figure 2.2: about the difference between the two columns). Environmental change, like air pollution and climate change may contribute to the existing damaging health effects of environmental factors. Yet there is a need for the development of methodologies to account for these effects (Martens et al., 1995; Leaf, 1989; Doll, 1992).

![Figure 2.2. World-wide distribution of deaths in millions in 1985 (Lopez, 1990).](image)

Health policy makers need analyses of questions on what the effective interventions are to improve prevention of infectious diseases, to improve survival, to improve reproductive health. They also like to know how effective and how efficient the interventions are to reduce morbidity and mortality in these various areas at the population level. Examples of areas in which health benefits are to be gained are
2.3.2. DECLINING MORTALITY STAGE

When mortality improves, population increases. Population growth is related to fertility and mortality changes. In this stage of the demographic transition death rates fall while births rates (yet), do not and population size increases. The interactions between population growth, economic development, and the environment are of vital importance for populations. This has been recognized since the early seventies (WCED, 1987; UNEP, 1997; Kiessling and Landberg, 1994).

Changes in population are important in two ways: by themselves and in relation to resource availability (Haines 1991; McNicoll 1992; Ness, 1993; Possas 1995; Whitmore 1990). These changes depend in an interrelated but different way on socio-economic development and access to services (Vianen, 1994; UNDP, 1995).

Population growth is an important pressure on society resources as well as on the basic environmental resources like food, water, air, and space (WRI, 1995). As populations are increasing the net outcome in terms of resource availability per capita will determine if and how quickly they will pass through the transition (Figure 2.1 arrows). An example is the food situation in Sub-Saharan Africa where food production in absolute figures has been rising during the population increase of the last decades (Rosegrant, 1995). Food per capita, however, has been declining with a consequential absolute increase in the numbers undernourished (Figure 2.3).

Figure 2.3. Absolute number of undernourished (millions) by world region and time period (Mitchell and Inigo, 1995). SSA = Sub-Saharan Africa, MEC = Mediterranean Crescent, E-Asia = East Asia, S-Asia = South Asia and LAC = Latin American and Caribbean
2.3.3. LOW MORTALITY STAGE

The intrinsic effect of the demographic transition is an increase in average age and a change in causes of death (McFaden, 1990; Uemura and Pisa, 1988; Ueshima et al., 1987). The elderly themselves are getting older but this contributes less to population growth and aging (Bongaarts, 1995). Simultaneously the years spent with disease seem to increase (Boshuizen et al., 1991; Crimmins et al., 1989; Fries, 1981; Heuvel van der, 1989; Kane, 1990; Olshansky, 1990; Verbrugge, 1989; Nusselder, 1995). Historical data (Alter and Riley, 1993; Riley, 1993), four modern long follow-up series (Riley, 1990) and cross-national data suggest a general pattern that years with disease increase with development as also the frail survive.

There are some complicating factors in this explanation. Firstly, earlier case finding by medical technology may lead to longer periods living with diagnosed disease, like in cancers (Parkin et al. 1994; Berrino, 1995) and in chronic conditions such as diabetes and chronic lung disease (Ruwaard et al., 1993). Secondly, disability weighting of diseases might influence how the increased period with diseases is appreciated. Applying the DALY weights shows a larger disease burden in life years in Sub-Saharan Africa as compared with industrialized regions (Ginneken, 1994). Different disability weighting procedures result in a kaleidoscopic picture of impairment, disability and handicap (McDowell and Newell, 1987) and the assessment of disability is problematic anyhow (Feinstein, 1986). Last, little is known on the dynamics of individual diseases and related disabilities at older ages (Olshansky, 1990; LaPorte, 1993; Barendregt et al., 1994).

As disease burden relates to the demand for health care, one can expect a decreasing demand for health care among the younger age groups. However, there is a necessity to maintain social and health services investments levels related to these groups at a sufficient level (Feacham et al. 1991). In addition to health care, socio-economic conditions and (secondary) prevention may contribute to postponement of severe disability (Heuvel van den, 1991; Fries, 1981; Bonneux et al., 1994; Niessen et al., 1993). Worldwide, also in developing countries, morbidity among the oldest may prove to be the most important factor in the total demand for social and health services (Kane et al., 1990).

2.4. GENERAL RESEARCH POSTULATE: MULTIPLE ROADS TO HEALTH

From the above, we conclude that there is substantial evidence that socio-economic development largely determines population health levels directly by influencing the immediate surroundings of people, their health behaviour and their access to services (Bairagi and Chowdhury, 1994; Kiesling and Landberg, 1994; Pappas et al, 1993; Winkelstein, 1993; Najman, 1993). Important other sectors contributing to improved standards of health, especially in the early stages of the transition, include food availability and drinking water supply (Gumper, 1984; Mertens, 1992; Esrey, 1991). Nutritional status has been an important factor in improving people’s natural resistance as well as by influencing birth outcomes and the survival of water- and airborne childhood infections (Crigg, 1989; Dreze and Sen, 1989; Pelletier, 1993; Alwar, 1992). In the last stage of the health transition, the main health determinants
are related to life style like smoking and hypertension (Bartecchi, 1995; Salonen, 1989; Tuemelito et al, 1991; Dobson, 1994; Casper et al., 1992; Collins, 1990). These risk factors, in turn seem to depend on socio-economic status (Marmot, 1994). Also, in this stage, health services seem to be a major determinant (Mackenbach, 1988). These often show diminishing returns with increasing inputs (Murray, 1995). Politically diverse populations with lower levels of economic growth have succeeded nonetheless in reaching high levels of health despite a low income per capita through high education levels, large scale public health measures and national cohesion e.g. Costa Rica, Kerala, Sri Lanka and China (Caldwell, 1993; Cooper, 1990).

A long-term integrated analysis should include the changing composition of the population, the increase in life expectancy and disability burden, and the demand / supply mechanisms. Presently, aggregated analyses only allow for crude changes in disease and disability (World Bank, 1993; Barendregt et al, 1994). Given broad objectives of the research, we have included a limited number of diseases and only by broad categories.

As these patterns of changes in population health are showing we postulate for our approach that there are multiple roads towards health within each stage of the health transition. This is the core theme of this book. Health determinants may have their impact on different levels of the causal web of disease occurrence (exposure, disease, and death). They may have an effect by themselves and in combination with other determinants and their effect varies in time depending on the presence of other determinants. Three examples are given for three countries in Figure 2.4. One route might be via the increase of physiological resistance, improving nutritional status and survival along the vertical axis, like in the Netherlands and England in the previous century (Gage, 1993; Schofield 1991).

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Figure 2.4. A conceptual representation: two pathways in the health transition, based on historical analysis and a semi-quantitative interpretation: the increase in life expectancy (= e on diagonal axis) by two ways of health promotion: prevention from exposure and increase in resistance to disease (adapted from Walle van der et al, 1992)
Another route, along the horizontal axis, in other societies or in other time periods, might be the reduction of health risks by the elimination of causes of ill-health, irrespective of the condition of their members, like in Japan in the beginning of the century. Here, large-scale hygienic measures, such as collective feces collection, took place and prevented people from falling ill. Other paths, or mechanisms, may be possible along other dimensions. Two other pathways might be the improvement of health behaviour in the general by education and promotion (Caldwell, 1993) or the improvement through the increase in personal income status. Both of these may lead to similar changes in the near surroundings and to similar behavior changes, as probably has been the case in Japan, Italy or the UK. The change in income status may, in addition, lead to health damaging changes in life style, such as smoking, like in the present societies in S-E Asia with fast growing economies. When literacy increases without sudden huge increases in income, as in Sri Lanka or the Netherlands around 1900 (Houwaart, 1991), the health damaging effects of socio-economic development may be less. Chapters 3 and 4 study the historical and future changes in health determinants and population health in three countries, for India, Mexico and the Netherlands. Chapter 5 discusses the historical decline in stroke mortality. The following chapters (6-9) will study the health service effects, prevention and treatment, on the occurrence of single diseases, for stroke and diabetes mellitus.

To summarize: the objective of the research is to describe and analyze the changes of (sub-) population and associated changes in health under varying socio-economic and environmental conditions in the past and in the future using demographic multi-state modelling techniques. This may include populations living in pre-industrial societies as well as those living at the highest known health levels. Such a long-term public health approach should account the main input-output relationships related to population health in terms of both environmental and societal resources. Inevitably, a modelling framework is needed to address all the changes in populations and population health at the same time in a consistent framework. It can be, if necessary, adapted to explore and test more specific policy questions, formulated as specific hypotheses in specific fields of medicine or in the treatment of specific diseases.

The next chapter describes such a generic multi-state modelling approach that can be used to address the various health issues that have been listed.
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Health transitions

CHAPTER 3

MULTI-STATE MODELLING OF DISEASE OCCURRENCE

3.1 SUMMARY

Introduction This chapter describes a generic multi-state modelling approach to population health that addresses the effectiveness and efficiency of population health interventions. The objective of this approach is to function as a general frame of reference to be used when one addresses specific questions.

Methods The main characteristic of such an approach is that it considers the main relationships between population health in terms of health states and flows between them. It includes both environmental and societal determinants in a dynamic and disease-specific way. This may include populations living with a low socio-economic status as well as those living at the highest known income levels. It may be used for analyses of population health in the past and in the future. This approach means a quantitative description of the disease epidemiology at the population level, taking into account the demonstrated confounding effects of the health determinants. There are many diseases and many intervention options; there are many ways to fall ill, many causes to die from, and a diversity of instances to actively intervene. There are many options to prevent people from falling ill, to improve recovery and the quality of survival of disease, and to avert premature mortality.

Results This chapter has shown how disease and death can be described in a generic multi-state model and how health interventions might be effective. It shows the building blocks for a generic framework for population health. It distinguishes and defines macro- and micro-determinants and multiple disease states. Next, it describes the practical and pragmatic approach in the mathematical implementation, distinguishing various transition probabilities between disease states and a number of aggregate outcome measures. In addition, it summarises approaches to demonstrate the validation, calibration, and robustness of outcomes and structure of the generic framework. The generic modelling approach is used in a number of studies. Chapter 4 distinguishes single disease states for a number of diseases together. It quantifies the contribution of health determinants to mortality decline in India, Mexico, and The Netherlands. Then, the next chapter analyses the decline in stroke mortality (chapter 5) using a stroke model with multiple states. In the chapters 6 through 8, the contributions of the health interventions to reduce the burden of stroke and diabetes are evaluated. In these latter cases, the descriptions of large single disease multi-state models may not show some of the elements of the generic approach. This application of the principle of parsimony is under the assumption that the indicated macro-determinants, such as nutritional status and socio-economic status, and other disease states do not influence model outcomes or the final conclusions.

Conclusion The modelling framework can be used to explore, to specify, and to analyse research and policy questions. This is both possible for use at the macro-level and to test more specific hypotheses in epidemiology, health economics, demography, and public health.
3.2. GENERIC APPROACH TO MULTI-STATE HEALTH MODELLING

Converging pathways in the health transition form the basis of the two postulates outlined in the preceding two chapters. These define population health by the presence of a specific pattern of health determinants and also distinguish slower and quicker roads to health. As formulated differently by Geoffrey Rose: there is no biological reason why a population should not be as healthy as the best (Rose, 1992). These statements are the equivalent of the more technical hypothesis that the model is generic. This implies that the observed empirical pattern of population change and burden of disease can be attributed to the levels and interactions of population and health determinants. It implies that the approach can be used to assess populations on various geographical scales, for different time periods, and with different degrees of differentiation of determinants, age groups, disease classes, and health services.

The population health macro-determinants represent those factors that influence the proximate health determinants. The selection of determinant categories is based on the evidence regarding their supposed quantitative importance throughout the health transition as reported in the literature. They are categorised in two groups: socio-economic determinants and environmental determinants. The two variables describing the socio-economic determinants are:

- Gross National Product (GNP) expressed in 1990 US-dollars. This parameter determines the available income per capita and the resources available for health services. Separate projections for the low-income countries are used in a distribution function to estimate the number of people below the absolute poverty line (World Bank, 1993);
- The female literacy level expressed as the fraction of the literate adult, female population. This parameter is computed as a delayed function of GNP and the Human Development Index (HDI) (UNDP, 1993-1995).

The variables describing the environmental determinants are:

- Food supply expressed in kilocalories daily intake per person. Input scenarios on the availability of food define the fraction of the population suffering from malnutrition. This fraction is calculated for the sub-populations that fall under the low socio-economic status categories (see below). These calculations are based on an empirical distribution function (FAO, 1987 & 1992);
- Safe water and sanitation access defined as the fraction of the population with proper access to safe drinking water and having sanitation, that falls under the low socio-economic status categories. In case of large discrepancies between the two parameters the safe drinking water coverage is chosen because this determinant is the most relevant of the two (Esrey et al., 1985, 1991);
Given these input scenarios for the macro-determinants, we now describe a general multi-state approach to population health. It consists of (Figure 3.1):

I. A **macro-level determinants component** describing the macro-determinants for population health: income status, literacy, safe water and food availability.

II. A **disease occurrence component** computes population, micro-determinants, diseases and mortality. Determinant, disease and mortality changes may be linked to all four macro-determinants under I.

III. **Population health effects component**: This is an output component that describes the quantitative and qualitative outcomes in relation to population numbers and disease burden.

IV. A **policies component** indicating the various options in the framework to change input scenarios and transitions probabilities to and from health states. The effectiveness of health interventions is computed changing the values of these parameters.

The dynamic population component includes the dynamics of disease occurrence at the population level through the inclusion of health determinants and disease
categories. As said, the health determinants are linked to income and literacy changes, food and water availability and service expenditures per capita by service category. All health states are divided in age groups. The selection of the size of the age groups is determined by the epidemiology of disease of the three health transition stages. Group members may leave a state by age group because of ageing. In addition, in each age group for each health state group members may change towards another single- or multi-determinant category. In turn, this latter category may lead to single or multiple disease states. The likelihood of transition from healthy to diseased or transition between disease states or from one disease state to another, a probability, is independent from the preceding events and depends on age, sex, determinant type and disease status. The probabilities in the disease model are a function of nutritional status and the level of curative health services. The numbers of persons that remain in disease prevalence states determine the level of permanent disability associated with the particular disease.

The disease burden attributed to a specific health determinant is calculated as life years lost because of mortality and weighted years lost because of disease. Additional outcomes can be calculated by adding specific components relating disease burden to additional economic impact like direct and indirect costs of illness (Drummond, 1986; Gold, 1987). The computed disease burden may influence, in a feedback loop, the health resources needed, but not their effectiveness.

The population health model simulates the number of persons suffering from diseases and the number of deaths related to these diseases. The disease figures are used to estimate the disease burden in the population. The computed death figures determine the overall age- and sex-specific mortality rates. The core assumptions related to the model structure and dynamics are listed in Box 1.

### Box 1: Core assumptions of the population health framework

I. The use of large population categories (in defining age groups, determinant types, disease groups and service categories) is justified in case of long term dynamics and population assessment at high aggregation levels (life expectancy, population size and total fertility levels) e.g. chapter 4. In the case of more specific research questions more detailed analysis is necessary (chapters 5-8).

II. There is a hierarchy in the causal contributions of health determinants. First level determinants are socio-economic and nutritional status. Next, depending on the level of these two, traditional risk factors have their effects.

III. Two economic status categories are used: above/below the internationally defined poverty line. Two nutritional status categories are used based on the availability of sufficient dietary kilocalories: above/below the basic metabolic rate by international standards.

IV. The contributions of each health determinant to the occurrence of disease and death can be quantified through corresponding relative risks, known from public health epidemiology.

V. The effect of health services can be modelled using a general effectiveness function. This function changes the modelled health determinants from a known minimum effect (based on data on subsistence health situations) to a maximum effect (from data from the healthiest populations).

VI. Change in mortality by disease group can be (almost) fully explained by 1) changes in broad and specific health determinants, affecting disease incidence and survival, and 2) the effect of preventive and curative services, affecting health determinants and disease survival, respectively.

VII. Parameter values from epidemiological surveys can be used in modelling population health if the survey setting is comparable to that of the involved populations e.g. population- or health-service-based.
Chapter 3

In the general framework, we define a number of health-related states by age group and by sex, influenced by health determinants. This will be described in detail in the next sections. The health state states are treated in a similar way as the overall population within the population and health model: inflows and outflows of the states combined with an initial value determine the contents of the state at a particular point in time. The flows concerning the disease processes are shown in the next sections. Ageing and mortality from residual causes are accounted for in all health states and are not included in the model equations.

3.3. MULTIPLE HEALTH DETERMINANTS

In the disease component, the health determinants represent the health risks people are exposed to. These health risks or micro-level health determinants partly exist in combination with macro-level determinants. These are defined in a health determinant component, which are reformulated in the specific health determinants categories in the disease component. In addition, as said, life-style related health risks, like smoking and high blood pressure can be distinguished. Criteria for selection of determinant types were 1) the availability of empirical evidence of a quantifiable relation with the occurrence of disease(s), the magnitude of the influence on mortality and morbidity levels in societies (Schofield et al., 1991; Walle van der et al., 1992; Winkelstein, 1993) and 2) the availability of epidemiologic data on disease and statistical demographic data on a population basis. We selected 12 determinant categories (Box 2 and Figure 3.3). The occurrence and clustering of multiple determinants within population sub-groups are taken into account. This results in a clustering of higher absolute risks of one particular disease as well as higher risks of other relevant diseases especially among children and the aged. Selecting the relevant combinations of the health determinants leads to the following categories of determinants:

1. High SES only
2. High SES & high blood pressure
3. High SES & smoking
4. High SES & high blood pressure & smoking
5. Low SES only
6. Low SES & malnourished
7. Low SES & malaria risk
8. Low SES & no safe drinking water
9. Low SES & malnourished & malaria risk
10. Low SES & malnourished & no drinking water
11. Low SES & malaria & no drinking water
12. Low SES & malnourished & malaria risk & no drinking water

Box 2: Health determinant categories within the generic framework. SES: socio-economic status.

The major health determinant is socio-economic status (Najman, 1993; Pappas, 1993; Marmot and Elliott, 1994; Velden vander et al. 1995). Given the objectives of the general framework, we choose to parameterize this determinant at a rather aggregated level. A high socio-economic status (SES) defined as either being literate and in the
low-income group, or being in the high or middle-income categories (Caldwell, 1973-1993) and living above the poverty line, as defined by international criteria (Heerink, 1994; Moreland, 1984; World Bank, 1992-1994 and Lim Chong Yah, 1991). Low SES is defined as being of the low-income category and illiterate or living below the poverty line. Hence, the basic equation is, for each moment in time:

\[ \text{high SES fraction} = \text{fraction high/mid income} + \text{fraction literate} \times (\text{fraction low income} - \text{fraction poor}) \] (4.1)

The fraction living below the poverty line is calculated using a fitted function (Figure 3.2) of GNP and the percentage of people below the poverty line, based on a cross-sectional sample of countries (World Bank, 1993-4). These percentages are country-based estimates from local surveys accounting for purchasing power differentials. There is a large variation depending, evidently, on the national political and economical context e.g. in Latin American countries there are relatively larger differences in income status than in the majority of the Asian populations. In the case studies this has been corrected somehow during the calibration phase by choosing the higher or lower coefficients, falling within the standard error. In fact, using the fitted function, one, implicitly, accounts for income distribution policies.

![Figure 3.2. Fitted function of GNP per capita and poverty level based on data from 28 countries (World Bank, 1993-94). Poverty = sufficient income to maintain a standard diet and fulfil daily basic needs. Upper and lower curves indicate uncertainty ranges based on standard error.](image)

Low SES determinant categories

The low SES population is divided into 8 additional determinant categories (see Box 2) containing (combinations of) nutritional status, drinking water supply and malaria risk but not high blood pressure and smoking. Considering the extremely low-income levels (less than US$ 2 per day), the latter two determinants are expected to influence the disease and mortality levels much less than the SES-related health determinants.
The most important low SES category is nutritional status (Binswanger and Landell, 1995; Pelletier, 1993-1995). Malnutrition prevalence is computed based on a function of the availability in kilocalories per capita daily food intake. Malnourished is defined as a lack of sufficient food intake in kilocalories i.e. less than 1.54 times the basic metabolic rate in kilocalories per day (1575 for adult males). Standards have been set by age, sex and body weight and also by pregnancy status. This distribution function is based on the empirically fitted relationship given by the FAO as reported in the fifth World Food Survey (1987). World food supplies and prevalence of malnutrition in low-income regions have been reassessed in 1992 (FAO, 1992). This resulted in adapted coefficients (see function below). In the module the percentage malnourished is calculated from the average food availability per capita as an input scenario. The fraction malnourished for each time step can be calculated as (Ashworth and Dowler, 1991):

$$malnourished\ fraction = \frac{1}{(1 + 0.01*\exp(4.31*food \ fraction))} \quad (4.2)$$

In this equation the food factor is a factor that is obtained in a function depending on food availability and age- and sex-specific daily need of food. For pregnant women in age group 15-45 an additional need of 138 Kcal per day is taken into account. The additional data in relation to the occurrence of diseases are based on the available international literature (Crigg, 1989; Dreze and Sen, 1989; Kielman and McCord, 1978; Pelletier, 1993 & 1995; Pinstrop-Anderson et al., 1993; Pinstrop-Anderson and Pandya, 1995; Sachdev et al., 1992; Vella et al., 1994; Niessen & Hilderink, 1997b)

Another important health determinant is access to safe drinking water. The provision of proper drinking water depends on the total public water supply investments. The population without public water supply and relying on private supply is regarded as having no access to safe drinking water and runs higher relative health risks of waterborne diseases. The input scenario for this parameter is based on international estimations on costs and economic growth (chapter 4, section 4.4). Sanitation facilities are included in these costs and are not considered to make an additional contribution in reducing the water-borne diseases. The independent preventive effect on disease occurrence seems very limited (Ahmed, 1994).

The next health risk modelled related to SES is the presence of malaria mosquitoes carrying malaria parasites. The fraction of the population exposed to such a malaria risk is based on internationally standardized estimations (Martens et al., 1995). This fraction is, again, influenced by health policy through vector control programmes. The fraction of malaria-affected population is also a function of socio-economic development.

**High SES health determinants categories**

The high SES population is divided into those exposed to smoking or not and those having high blood pressure or not. Scenarios for these determinant categories are sex- and age-specific and based on empirical time series. Trends are extrapolated but still subject to health services effects i.e. preventive measures. It is assumed that
people who reach only this level of socio-economic development will be exposed to these two health risks. The input series for smoking levels are based on estimations of the tobacco production since 1900 (WRI, 1995). Although the occurrence of related health problems has been rising first in the sixties and seventies in Europe, the mortality figures are now rising worldwide although much more among men than among women (Peto, 1992; Bartecchi et al, 1994-1995; McKenzie et al., 1994). Input data are based on existing survey data and reviews or existing models (Tunstall, 1994; Ruwaard et al., 1993; Niessen et al., 1993). The prevalence of smoking is increasing and reaching very high levels (up to 70-85%) in large areas of the world, especially in countries with low-income levels. There is a world smoking prevalence estimate by WHO of 52% for men and 10% for women and there are estimates for e.g. China of even 61% for men and 7% for women (Stanley, 1993). The relationship between smoking and a large number of diseases is clear and has been quantified (Jackson and Beaglehole, 1987; McGovern et al, 1992; Pearson et al., 1993). In case of mortality change, one often observes a change in health risk prevalence that changes disease incidence, but also a change in disease survival. There might be two types of independent changes, as a consequence of prevention interventions or an increase in survival due to curative activities (Farchi, 1984; Dobson, 1994; Bonneux et al. 1996). The potential health gain by reducing health risk prevalence is large (Gunning, 1989; Tsevat et al., 1991; Grover et al., 1994). The epidemiological input data used are based on existing surveys or existing models (Tunstall et al., 1991, Bonneux et al., 1994). The relationship between high blood pressure and cardio-vascular disease, ischemic heart disease or stroke, has also been quantified (Dyken, 1984; Klag et al., 1989; McGovern & Beaglehole, 1987; Casper et al., 1992; Whelton, 1994). There are also estimates of the potential health gain by treatment or prevention (Gunning-Schepers, 1989). Data are based on existing survey data, reviews or existing models (Tunstall et al., 1991, Niessen et al., 1993, Ruwaard et al., 1993).

Combining health determinants
The various combinations of the health determinants are depicted in Figure 3.3. Assumed is an independent occurrence of most categories except for the combination of malnutrition and no access to safe drinking water where a correlation/clustering factor of 1.1 is used. This figure proved to be the maximum possible still explaining empirical data (World Bank, 1993). In this way a clustering of health determinants among the populations with low economic status can be simulated. Criteria for selection of determinant types are 1) the empirical evidence based on the epidemiological literature on a quantifiable relation between the health determinant(s) and disease and mortality levels in societies (Schofield et al., 1991; Walle van de et al., 1992) and 2) the availability of population-based statistical data.
3.4. MULTIPLE DISEASES

The second part of the population health framework contains the health states that represent the number of people afflicted by the occurrence of a disease. The disease groups are selected based on 1) their empirically estimated contribution to mortality and 2) disease levels in societies as is known from international data bases (Table 3.1) (Ghana Health Assessment Project Team, 1981; Mosley, 1991; Thom, 1994; Parkin, 1985-1994). Some of the more important causes of disease and mortality have not been modelled explicitly (like tuberculosis and accidents) as their occurrence has not been documented to relate to particular health determinants and/or interventions, except to the general category 'socio-economic development'. Other diseases seem to occur at a more or less constant rate in populations like some neuro-psychiatric disorders (Cowley, 1993). Both these two categories of diseases are included in the 'residual mortality' category. The resulting selection of the specific diseases included in the general framework is as listed in Table 3.1.

The size of the sub-populations defined by the twelve determinant categories determines the population at absolute risk for these diseases. The absolute level of the annual disease risk is the inflow from the exposed population towards the disease states. The absolute risk is obtained by a multiplication of a constant disease-risk for the unexposed populations (the ‘natural’ incidence), and the excess relative risk (RR) depending on the determinant category and the disease type. The base disease-risk is calculated from the population-attributive risk fractions based on the epidemiological literature (Walter, 1976). In chapter 1 it is described how these fractions equal the risk-attributable incidence that defines the transition from a
healthy state to a disease state. The RR represents the excess chance of getting a
disease due to a specific health risk as compared to a reference population.

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases</td>
<td>Gastro-enteritis</td>
</tr>
<tr>
<td></td>
<td>Acute respiratory infections</td>
</tr>
<tr>
<td></td>
<td>Measles</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
</tr>
<tr>
<td>Maternal and perinatal diseases</td>
<td>Prenatal mortality</td>
</tr>
<tr>
<td></td>
<td>Maternal mortality</td>
</tr>
<tr>
<td>Cancers</td>
<td>Lung Cancers</td>
</tr>
<tr>
<td></td>
<td>All other cancers</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Circulatory and degenerative</td>
<td>Acute Infarctions</td>
</tr>
<tr>
<td>diseases</td>
<td>Chronic Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Residual diseases</td>
<td>Remaining mortality</td>
</tr>
</tbody>
</table>

Table 3.1. Disease categories within the generic model framework.

The values for these RRs are derived from the epidemiological literature (Ruwaard et
al., 1994; Niessen et al, 1995). The estimates for malaria are based on the outcomes
of a more detailed infectious disease model described elsewhere (Martens, 1995).
The overall disease risk is determined by a base disease risk multiplied by the RR for
the involved health determinant and involved disease, by age and sex. The basic
equation for the disease determinants for all the determinant- and disease categories
is as follows:

\[
disease \text{ risk} \_\{sex,age,exposure,disease\} (t) =
\text{basedisease} \text{ risk} \_\{sex,age,disease\} \times \text{RR} \_\{sex,age,exposure,disease\} \times \text{exposed population} \_\{sex,age,exposure\} (t)
\]

\(\forall sex \in \{\text{male, female}\}, age \in \{1,2,\ldots,5\},\)
\(exposure \in \{1,2,\ldots,12\}, disease \in \{1,2,\ldots,10\}\)

Here, the relative risk (RR) is a constant and the exposed population changes in time
depending on births and deaths. The equation 4.4 defines the flow from the health
determinant category to the disease states. It can be divided into three events (cp.
Figure 1.4). The first is the event directly related to the absolute disease risk and is the
case-fatality rate (CF), defined as the probability of dying during the acute episode of
the disease. The levels of the case-fatality are age, sex and disease-specific. They are a
function of the level of curative health service expenditures per capita. For each
disease minimum and maximum values for the case-fatality are defined. These
correspond to the lowest respectively highest known levels reported. A cure-
effectiveness function determines the actual CF in between the extreme values:
The second possible event is recovery within a year after becoming incident. Similar to the case-fatality, the level of recovery is determined by a cure-effectiveness function modified by the level of curative health service expenditure. The third event is entry into the disease state. They become chronically ill for the involved disease. The event is assumed irreversible. Next, there are two possibilities of leaving these disease states. The probability of dying is based on an overall base mortality risk and a disease-specific delayed mortality risk. This, late, surplus mortality risk is defined as the ‘late’ mortality risk. This fraction is likewise based on a minimum and maximum value and influenced by the effectiveness of curative health service expenditures. The second possibility of leaving the first disease state is getting another disease. Especially among the elderly but also among those with already respiratory disease this is frequent. In the general framework, ‘double-diseased’ states have been defined to include the eight most frequent combinations of chronic diseases. The events related to entry of this double diseased state are similar to getting a first disease: curing and dying are treated similarly, using the same functions and the same absolute values as for single diseased. The total disease-specific mortality figures by sex and age related to these eight diseases are obtained from the single and the double disease states. They are used to compute the survival of the population.

The yearly ageing of the various sub-populations depends on the length of the age group and is roughly the inverse of that length in years (for example the ageing out of age group 0-5 is 1/5). Because of the non-uniform mortality distribution within the age groups, it is adapted to the distribution of people over the age group. This distribution is represented by the fraction of people surviving up to last year of the age group (in the example up to 5 years) divided by the length of the age period. Thus:

\[
\text{ageing}_{\text{sex, age}} (t) = \frac{(1 - \text{total mortality proportion}_{\text{sex, age}})^{\text{length of age period}_{\text{age}}}}{\sum_{i=1}^{\text{length of age period}_{\text{age}}} (1 - \text{total mortality proportion}_{\text{sex, age}})}.
\]

Here, ageing is the proportion of survivors in each age category, i.e. those that move on to the next age category.

At last, total mortality is discussed. It consists of three components. The disease mortality fraction that is the mortality explained by the known disease epidemiology. This is based on the combinations of the various macro- and microdeterminants and the subsequent occurrence of disease and death. The second component is the maternal mortality fraction. This is calculated by a multiplication of the number of women of the ages between 15 and 45 years, the number of births and a maternal mortality risk based on the level of curative health care services. The third and last component is ‘residual mortality’. It is a, presumably biological, baseline level of
mortality, sex and age-specific, defined as the yearly mortality that can not be related to a particular cause. This mortality fraction is quantified using a golden standard life table.

**General outcome measures**

The most used general outcome measure that combines morbidity and mortality is disability-adjusted life years (DALYs) per thousand (World Bank, 1993). In this approach the time lost with disease, as acute or chronic case, is added to the time lost due to premature death as compared with the standard life table North (Murray, 1994). The weighing of the contribution of the different diseases to a loss of health is done separately for acute episodes and for chronic, prevalent, cases. The duration of an acute period depends on the disease: in general two weeks for infectious diseases and one month for chronic diseases. Chronic cases are counted as lasting a whole year. The time spent with disease is weighted by degree of related disability (Murray, 1994).

We adapted this approach to calculate the disability-adjusted life expectancy (DALE) (Niessen en Hilderink, 1997). This computation accounts for both the loss of health through premature death as well as through disease. It is an aggregate measure. To calculate the number of life years for the computation of the DALE, the age of death is compared to an assumed estimated average upper limit of 82 years for men and 88 years for women at birth (Murray, 1994). The origin of the losses of health by category can be obtained from the population health framework. As it distinguished the 12 subpopulations by health determinant, the model records the relative contributions of each of the determinant categories to the occurrence of disease and death. In this way, the years lived and the average loss of health can be clustered into four categories, three related to health determinants, all measured in DALE years. These are:

1. the net healthy years lived per average lifetime and the loss of life years by three clusters of health determinant:
2. loss due to high SES and life-style-related health determinants such as smoking,
3. loss due to low SES only,
4. loss due to environmental determinants, such as food, water and malaria in combination with low SES.

The occurrence of diseases is accounted for in the last three categories while the category 'mortality from residual diseases' is considered in a residual category.

Now, after having defined the framework, the next section deals with the actual practical implementation of the model approach.

### 3.5. MODEL IMPLEMENTATION AND VALIDATION

This section distinguishes first four concepts used in relation to model validation, relates examples from the five studies reported in the later chapters and describes validation of the generic framework.
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Validation is the process of establishing the adequacy of a given mathematical model in representing a given structure e.g. a disease process. There is a fundamental trade-off in testing a model for validation. Using a very stringent test one will need a large number of iterations in the development process and the final result will be too complex and yield limited insights. Using a simple test, most models may pass, poorly representing the involved problem, and turn out to be useless for solving the problem. Validation takes place during the whole of the process of model development. Constantly, one may seek arguments in support of the model but also for arguments to falsify the model. One may argue that one can accept a model, as long as it is impossible to falsify the model. Usually one starts with the simplest conceivable model and extends the model until it passes the validation tests. In the end, the modeller’s skill and intuition will have mostly determined the final trade-off between simplicity and adequate representation.

Next, four closely related concepts are described: conceptual validation, calibration, external validation, and internal validation. They are described in the same order as in developing a model, although most may be used throughout the whole process. External validation usually is the most prominent feature in validation. There is a fifth concept, operational validity that is often distinguished. This is the appropriateness of the model to give answers to the raised question. The latter is part of a broader discussion on the general scientific approach and is not dealt with.

3.5.1. DEFINITIONS OF VALIDATION

Conceptual validation

Conceptual validation can be defined as the process to verify the used assumptions and concepts against existing scientific theories. This should be carried out in dialogue with experts in the involved field. It is the final judgement of the expert in the field that may lead either to acceptance or rejection of the chosen model approach. This validation is very much dependent on the problem and the domain involved. It is difficult to give general statements on this. Each disease, depending on the level of detail of the research question, will turn out to have its own characteristics to account for. Experts may differ in opinion. There are a number of structured ways to establish a consensus or to reach partial agreements e.g. the Delphi method.

Empirical calibration

Calibration can be defined as varying model input values in order to match model output values to empirical data from other sources. In the definition of parameters a model may remain close to empirical data and already established demographic and public health definitions. Still, given the model complexities, level of detail, and need for consistency, it often is necessary to adapt some input variables to be able to
reproduce existing data on population, disease, and mortality. When input parameters have large uncertainty ranges, calibration is used to limit these ranges.

**Example 1.** A simple one-year state model for a single disease can describe the incidence, prevalence, and mortality from a disease. Fitting these in a consistent set reproducing the actual epidemiological data for these three parameters is a calibration process. An important assumption is that disease related events (remission, mortality) occur in the first year of the disease. This can be because of the biology of the disease, but more often, it is an assumption to just be able to describe the epidemiology for one particular year. It is usually true for acute diseases that either lead to death or recovery within the time span of one year. This often might not be the case for chronic diseases like cancers or cardiovascular conditions. The calibrated results give an adequate reproduction of empirical data for the involved year. The values and the used model structure do not necessarily describe the disease process in time, in a cohort manner, in an adequate way. This is not a problem as long as the objective is the description of the disease burden for a given calendar year. When one would like to assess the effects of interventions on the disease process, the simplified structure might become a source of inconsistencies.

**Example 2** Extending this model to a multi-state model would need adaptation in a two ways. It might need adaptation of the survival parameters to account for the additional disease stages or it might be an adaptation to account for the influence of other health determinants or diseases. When the number of states is limited and relatively basic mathematical functions are used, variable values also in this phase may be adapted in a calibration process to fit at least some external data. Variables whose values can be adapted during the calibration procedure are selected from the ‘free’ variables, i.e. those variables whose values are not exactly known or may have a range of plausible values. Formally, one could identify first, in a systematic multivariate sensitivity analysis, the most influential parameters. The variables that can be used for calibrating model outcomes can be the relative risks, hazard rates, or the residual mortality risk in each state. The intermediate parameters may not be used for calibration, as they may be a function of other parameters. Some parameters may, theoretically, be considered to represent the exact value, and cannot be varied, such as the baseline level or annual disease-specific mortality rates. The remaining parameter values may be varied within in stated range of e.g. ten percent to fit the empirical data.

**External validation**
Calibrated model variables can be compared with remaining empirical data for the similar study period and similar regional populations. This is called external validation of model outcomes. This is usually the core of the validation activities. Formally, one could express this in some ‘goodness-of-fit’ measure. These variables could be the crude output figures from a population model like total births, birth and death rate, life expectancy or population size. These can be compared to UN or other general statistical summary data. Additional parameters may be the same as listed in the previous section as long as they are not used for calibration: intervention
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costs, expenditure, effectiveness of interventions, relative risks, residual mortality risk.

More specific figures to use for validation can be the actual computed life expectancy of high or average risk groups (like the malnourished), disease-free life expectancy, based or not based on increased general mortality risk (like stroke survival) or disease-free expectancy (e.g. stroke free life expectancy). Actually, one should be looking for as much external data as possible for external validation. This will depend very much on the state-of-the epidemiology in the particular field.

Internal validation

Once calibrated, the model is run and tested to compare its intermediate outputs for consistency and to other existing data from empirical surveys, models or estimates from expert groups. We define this as internal validation.

Example 1

It is fundamental that all input population figures should be accounted for in the model. This means that the population totals, including births can be traced in the distribution across the various disease and mortality states. Hence, the sum of the living and births together should be equal to the sum of susceptibles, diseased and dead in all time steps. When the flows between the states are not adequately accounted for this may turn out not to be the case i.e. one loses people during the next time steps or one has too large a number of centenarians.

Example 2

Disease incidences and disease-specific mortalities are relatively difficult to quantify, especially at the more aggregated population level. One can test the consistency of the multi-state model values by eliminating the disease-specific states and calculating directly the excess total age and sex-specific mortality by risk category. This can be done e.g. with the disease-specific figures for the malnourished category computing average overall excess mortality by age and sex. For various health determinant categories, this will yield the age-specific, possibly also sex-specific, overall mortality risk (see below in Table 3.2).

Example 3

Rapid changing in input values may or may not be reflected in model outcomes. Sometimes, an existing model may not adequately simulate dynamics of disease occurrence as it uses too large time-intervals. One can test a model by introducing, manually or systematically, sudden changes in model inputs to see the effects on outcomes. The acceleration in incidence increase, and concomitant mortality, of e.g. infectious disease may not be simulated through a model with large time steps. A basically similar example might be the sudden changes in births. These can not be simulated accurately due to the use of too large age groups of women of the fertile age. In case of a baby boom, like after a war or recession, may not be reflected in perinatal and infant mortality rates when one uses five-year age groups. Its effect may be ‘diluted’ over a period of 5 years (the size of the first age group).
3.5.2. VALIDATION OF THE GENERIC FRAMEWORK

In the study presented in chapter 4 we have used empirical data for historical calibration of the model outcomes for periods of several decades or longer. We extracted these data from four types of sources:

- national and international data registrations as reported or made available, summarised by different levels of aggregation (national, regional),
- population-based epidemiological surveys as reported in the literature or as used by other models by different levels of aggregation (national, regional),
- clinic-based research as reported in the literature and
- other surveys at the population level in the field of the social sciences.

Mostly, we used the data as input for the population health model without further calculation, interpolation, or smoothing. As can be expected, one finds many different parameter values in the literature. Our selection is based on the criterion that the involved study population should be similar to the defined (sub-) population in the model. This means that they relate to e.g. the high or low SES categories of the health determinants and corresponding diseases. One important exception is the use of data on acute respiratory infections and diarrhoeal disease for the chosen values for disease determinants, relative risks, case fatality and late mortality by age group, sex, determinant category and disease group as well as for the literature sources (Niessen and Hilderink, 1997).

Variables whose values can be adapted during the calibration procedure are selected from the free variables, i.e. those variables whose values are not exactly known or may have a range of plausible values. In a systematic multi-variate sensitivity analysis, the following parameters in the framework appeared to be most influential:

- female literacy coverage, in correlation with GNP,
- the percentage of people below the poverty line,
- the absolute GNP levels,
- the curative expenditure and the effectiveness function for intervention options,
- relative risks,
- base-risks for mortality.

The first two parameters of this list are not used for calibration as they are assumed a function of GNP. The last parameter is considered to represent the biological lower limit to the age-specific risks of mortality and is not varied either. The remaining three parameter values were varied within in range of ten percent to fit the empirical demographical time series. Seven calibrated model outcomes compare with the empirical time series for the period 1900-1990: the human development index, total births, crude birth and death rate, life expectancy, and the resulting population size. During the process, within the population model, the estimated number of
perinatal deaths had to be increased to fit the population time series. This was effectuated by including the newborn in the malnourished determinant category. Hence, the simulated number of total deaths exceeds the historical estimates. During computation this malnourished fraction may disappear as food availability improves and, consequently, perinatal mortality lowers. The acceleration in increase in population could not be reproduced more accurately due to the large age groups used. The steady drop in perinatal and infant mortality that has been observed shows only up as a relatively slow increase in population. This is due to ‘dilution’ over the period of the size of the first age group.

Internal validation of the generic framework

Once calibrated, the model is run and tested to compare some additional intermediate output to other existing data from empirical surveys. This is defined as internal validation and shows the consistency of the model values across the various level of the model. In the generic framework, two flows related to the disease states, disease incidence and disease-specific mortality are relatively difficult to quantify for many populations, especially at the aggregate population level. We tested the consistency of the model values by eliminating the disease-specific states and calculating directly the excess total age and sex-specific mortality by determinant category for the year 1990. When dividing these by the figures for corresponding reference categories, the high SES and low SES age and sex-specific mortality, one computes in fact ‘simulated’ relative risks, determinant-attributable figures on the excess risk of total mortality by age and sex category (Table 3.2). The top half of the table gives the values for the resulting relative risks for each health determinant category. The lower half of the Table 3.2 shows the corresponding values found in the literature. The table shows that the framework produces relative risks in the same order of magnitude as reported in empirical surveys. One can also observe an appropriate age-gradient in the low SES categories. The empirical relative risks for malnutrition is based on a large number of study populations throughout the world (Pelletier, 1995) and is in between the simulated values. This can be expected as malnutrition clusters with a number of other health determinants. The reported relative risks for lack of safe drinking water shows a large range, although we selected the values from the most rigid surveys (Esrey et al, 1985). Other ways to internally validate the model are possible but are not elaborated as they depend very much on the available external data. Computing mortality decline in different historical populations and at different scales can also test the model framework. If this turns out to be possible, this contributes to the structural validity of model dynamics and genericity. We used the model for three countries: India, Mexico, and The Netherlands (see for details chapter 4).
### Sensitivity of outcomes to health determinants levels

The robustness of a model to the input scenarios can be demonstrated by computing their relative quantitative effect on outcome measures. This indicates that the model equations and input values give an appropriate quantitative description of population health in relation to its determinants.

*Figure 3.3* shows some test results for population size and life expectancy to illustrate the robustness of the generic model version in relation to four scenarios for two clusters of determinants (Niessen and Hilderink, 1997b). A first cluster combines SES (national income, income status, income distributions and literacy) and health services level (prevention plus curative services). The second cluster includes food

---

**Table 3.2:** Simulated (A) and empirical (B) relative risks for mortality by health determinant, age & sex.

<table>
<thead>
<tr>
<th>Determinant</th>
<th>High SES</th>
<th>BP</th>
<th>NIC</th>
<th>NIC + BP</th>
<th>Low SES</th>
<th>NUT</th>
<th>MAL</th>
<th>WAT</th>
<th>NUT</th>
<th>MAL</th>
<th>WAT</th>
<th>NUT + WAT</th>
<th>MAL</th>
</tr>
</thead>
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<tr>
<td>age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1</td>
<td>1.6</td>
<td>1.9</td>
<td>1.9</td>
<td>2.5</td>
<td>2.2</td>
<td>2.8</td>
<td>3.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-44</td>
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<td>2.6</td>
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<td>2.2</td>
<td>1.3</td>
<td>2.5</td>
<td>1.5</td>
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<td>2.8</td>
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<td>1.7</td>
<td>1.2</td>
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<td>1.1</td>
<td>1.3</td>
<td>1.4</td>
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</tr>
<tr>
<td>75+</td>
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<td>1.4</td>
<td>2.5</td>
<td>2.8</td>
<td>1.1</td>
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<td>2.2</td>
<td>2.8</td>
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</tr>
<tr>
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<td>2.6</td>
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<td>2.0</td>
<td>1.2</td>
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<td>2.3</td>
<td>2.5</td>
<td></td>
<td></td>
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<tr>
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<td>1.1</td>
<td>1.9</td>
<td>2.0</td>
<td>1.1</td>
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<td>1.6</td>
<td>1.2</td>
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<td>1.8</td>
<td>2.1</td>
<td>1.0</td>
<td>1.3</td>
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<td>1.1</td>
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<td>1.4</td>
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</tr>
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<td>1.6</td>
<td>2.1</td>
<td>2.5</td>
<td>1.1</td>
<td>1.4</td>
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<td>1.5</td>
<td>1.2</td>
<td>1.5</td>
<td>1.6</td>
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</tr>
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A. Simulated relative risks

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<thead>
<tr>
<th>Determinant</th>
<th>BP</th>
<th>NIC</th>
<th>NIC + BP</th>
<th>NUT</th>
<th>MAL</th>
<th>WAT</th>
</tr>
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<tbody>
<tr>
<td>age</td>
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<td></td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>1.54</td>
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</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>75+</td>
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<td>1.44</td>
<td>NA</td>
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</table>

B. Empirical relative risks.

NA= not available. SES: Socio-economic status; BP = High blood pressure; NIC = smoking; NUT = malnutrition; MAL= Malaria exposure; WAT = no safe drinking water. Sources: High blood pressure: MRFIT-study (Marmot et al., 1994); * Chicago Heart Association Detection Project (Marmot and Elliot 1994); Smoking (Peto et al. 1992); High blood pressure & smoking: MRFIT-study; Malnutrition (Pelletier, 1995); Water risks: (Esrey, 1985 ); Malaria risk: Kisumu & Garki project (Najera et al., 1993).
availability per capita and access to safe water supply over a similar period. First, the effects are shown in a scenario of the two clusters combined as the reference scenario. Next, for each individual cluster the scenarios and outcomes are shown. The fourth scenario assumes a status quo (constant initial values) for both clusters of health determinants. All other parameter values have been kept the same as in a historical calibration in the reference scenario.

One can observe that, with an almost zero growth in life expectancy, there is still a considerable population growth due to high fertility (children per women, as input values). In addition, some important observations on the generic nature of the effects of health determinants in relation to population can be made. The net health effects of the two types of clusters on life expectancy are considerable and are of the same order of magnitude. Also the health effects of the scenarios for two clusters combined 'explain' almost all increase in life expectancy. At low life expectancies, there are more children born per women. In spite of the lower number of fertile women and children surviving, there is still a population increase. A concomitant increase in life expectancy causes an even higher population increase rate.

Figure 3.3. Sensitivity of population size and life expectancy to changes in health determinants.
3.6. CONCLUSION

This chapter describes the building blocks for a generic framework for population health. It distinguished and defines macro- and micro-determinants and multiple disease states. Next, it describes the practical and pragmatic approach in the mathematical implementation, distinguishing various transition probabilities between disease states and a number of aggregate outcome measures. In addition, it summarises approaches to demonstrate the validation, calibration and robustness of model outcomes and structure.

The generic multi-state approach has been applied in studies in the next chapters. Chapter 4 distinguishes single disease states for a number of diseases together. It quantifies the contribution of health determinants to mortality decline in India, Mexico and The Netherlands as part of a larger programme at the Dutch National Institute. The next chapter analyses the decline in stroke mortality (chapter 5) using a multiple state model. Next, chapters 6 through 8 present the contributions of various health interventions to reduce the disease burden of stroke and diabetes. In these latter cases, the descriptions of the large single disease models do not show a lot of the elements from the generic approach. Here, the principle of parsimony rules: the assumption is that the excluded parameters, such as the determinants nutritional status, socio-economic status or specific health risk factors, as well as the presence of other diseases do not influence model outcomes nor the final conclusions.
REFERENCES

18. Drummond MF (1987), Stoddart GL and Torrance GW: Methods for the economic evaluation of health care programmes. OUP.
Chapter 3


SECTION III

MULTI-STATE MODELLING
CHAPTER 4

DETERMINANTS OF MORTALITY DECLINE

4.1. SUMMARY

Introduction The importance of the contribution to the mortality decline of improvements in nutritional status, safe water supply, sanitation, income and literacy status, and health services is subject to recurrent and heated debates. The chapter examines how multi-state modelling can synthesise the results from epidemiologic and demographic studies to estimate the effect of each health determinant to changes in differential mortality in India, Mexico, and The Netherlands.

Methods The applications use the generic model framework. Input data on health risks are based on historical figures. The input figures for these three parameters are selected from studies on comparable sub-populations. The calculations reproduce the historical demographical figures of the three countries on population size, crude death rates, crude birth rates and life expectancy at birth. Model outputs have been tested for their validity and consistency. Calculated excess total age- and sex-specific mortality risks by health determinant are similar to those reported in the literature. Calculated annual disease-mortality rates, however, were not always consistent with historical time series.

Results Adding official future scenarios, the generic model framework shows that it can account for competing, multiple health determinants and multiple diseases, describing historical mortality declines in the three countries.

In the Netherlands, literacy and increases in SES lead to considerable high health level even without modern health care. With the introduction of modern care, life expectancy increased even more, but with diminishing returns. In Mexico, simultaneous increases in SES and access to modern health care lead to a fast increase in health levels. In India all improvements in health determinants seem to be there but increase at a slower rate. Two model experiments show the net estimates of the contribution of safe water supply and health services as a function of the level of other health determinants.

Conclusion The outcomes and model testing show that improvements in health determinants have three distinct origins: 1) the substitution and competition of health risks and diseases causing a certain inertia in the improvement of health 2) the prevention of cohorts becoming ill and, 3) increased survival after entering disease states. There are no unique solutions in the quantification of the role of health determinants in the mortality transition for specified populations. The contribution of each determinant is always depending on the level of other health determinants. Each population is bound to follow its own path in the transition by the country-specific pattern of determinants. Time series of historical disease-specific mortality rates should be used for further calibration and validation of model outcomes. This will result in a reduction of uncertainties in parameter values. Many more applications are possible, especially for the design of optimal strategies in the improvement of health determinants.
Chapter 4
4.2. INTRODUCTION

This chapter describes the use of the generic modelling framework to analyse the historical decline in mortality in three countries i.e. India, Mexico and the Netherlands. These case studies have been part of a larger programme at the Dutch National Institute (Swart et al., 1995; UNEP, 1997; Niessen and Hilderink, 1997). The countries were selected by four criteria: (1) each population presently living in a different stage of mortality decline, (2) the availability of demographic data, (3) different population sizes, and (4) their relevance for the UN’s international reporting (Swart et al., 1995). The case studies were selected to test our methodological postulate regarding the generic use of the framework. In addition, the assessment results of the case studies are given and compared. It shows the contribution of health determinants in mortality decline.

After an introduction, the scenario methodology for the health determinants is described and the sources given. Next the estimates of their contribution to mortality decline are given and compared. Then two model experiments are reported to show the dynamics of disease substitution and competition. Last, a number of conclusions are drawn on the relationship of health determinants and disease occurrence.

Table 4.1 shows the specific demographic pattern in the three countries. India shows the demographic pattern of a late first transitional stage (chapter 2) with still a high level of fertility and mortality. Mexico finds itself in the second stage. Death rates have been declining for many decades but the changes in fertility are lagging behind for relatively long time i.e. some 30 years. The Netherlands, in the next stage, have seen an early decrease in mortality levels and a relatively slow decline in births rates to below replacement level. The crude death rate rises in the Dutch population as it is ageing.

<table>
<thead>
<tr>
<th>Population figures by country</th>
<th>Calendar year</th>
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</thead>
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<tr>
<td></td>
<td>1900</td>
</tr>
<tr>
<td><strong>India</strong></td>
<td></td>
</tr>
<tr>
<td>Crude death rate (0/000)</td>
<td>42.6</td>
</tr>
<tr>
<td>Crude birth rate (0/000)</td>
<td>49.2</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>23</td>
</tr>
<tr>
<td>Children/women</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td></td>
</tr>
<tr>
<td>Crude death rate (0/000)</td>
<td>45.0</td>
</tr>
<tr>
<td>Crude birth rate (0/000)</td>
<td>49.0</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>33*</td>
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<tr>
<td>Children/women</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>The Netherlands</strong></td>
<td></td>
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<tr>
<td>Crude death rate (0/000)</td>
<td>25.6</td>
</tr>
<tr>
<td>Crude birth rate (0/000)</td>
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</tr>
<tr>
<td>Children/women</td>
<td>6.1</td>
</tr>
</tbody>
</table>

In each case the modelling framework is used to analyse mortality changes for the populations from the first stage of the health transition onwards starting in 1900 for two countries. It explores the possible futures for India and Mexico based on scenarios. In case of the Netherlands we tested only a historical simulation, from 1860 to 1990, as this country has completed the last known stage of fertility and mortality change. We used historical input scenarios for population health determinants and the related future scenarios internationally available.

The chapter describes first the methodology regarding the health determinants scenarios followed by the associated results regarding population change and disease burden. It is discussed for each case how the health transition pathway can be mapped out. Last, it arrives at a synthesis and conclusions regarding the general applicability of the modelling framework.

4.3. SCENARIO METHODOLOGY

Here, we describe first the general methodology of scenario development. The next section gives the details by country. As said, these scenarios are based on internationally available data and estimates. Each scenario parameter is consistent with the levels of the other parameters. This means that the GNP scenarios are taken as the basis for the changes in literacy, health services, water supply, and food availability. As the World Bank GNP scenarios are all optimistic the projected changes in the parameters are also optimistic. They are based on scenarios that haven been part of the Global Environmental Outlook reports by the UN Environmental Programme (Swart, 1996). The same methodology has been applied uniformly to the three case studies (see tables in the next section for the country scenarios). These are historical and future input assumptions regarding the changes in water availability, food security and socio-economic changes as expressed in literacy, gross national product, and changes in total health service expenditure level. We describe them by input scenario parameter.

Gross national product projections The economic scenarios are based on projections available from the World Bank (1993). They are expressed in percent growth of the gross national product in US$ 1990.

Changes in the number of people below the poverty line The (future) changes in the number of absolute poor are estimated using the fitted function of GNP and percentage of people below the poverty line (chapter 3). We used the GNP figures expressed in 1990 prices. The poverty threshold at this price level amounts to an annual 420 US$ on a purchasing power parity basis. The population below the poverty line is estimated using a function of poverty distribution and GNP for low-income countries categories (chapter 3).

Food availability The food scenario is associated with the GNP scenario for developing countries. It is expressed in terms of number of available kilocalories per person per day. It is calculated using a general increasing function between GNP and food demand in kilocalories i.e. the “Engel” curve (Alcamo et al. 1994) and the Agrostat data (FAO, 1992, Rosengrant, 1995).
**Water supply.** The water supply scenario is calculated assuming a full water and sanitation coverage by the year 2050. This is set as a policy as this is usually the case in the implementation of this type of infrastructure. Full coverage seems to be economically feasible given 1) the favorable economic scenarios used of an average 2.3% growth per capita until 2025 in the low- and middle-income countries combined (World Bank, 1994), 2) a constant total percentage of investments in water and sanitation of 0.4% of the GNPs, and 3) the demographic scenarios as given in the tables (UN, 1992). For these scenarios we had to make a number of separate, not included, costs assumptions. They are based on:

- the costs of a technologies mix for urban populations (50% of the population for 200US$ per capita, 25% of the population for 100 US$ and 25% 20 US$ per capita, and low-cost technology for rural populations (=30% of the population).
- the water access scenarios by UNEP (1997). Here, about 120 million people, worldwide, are assumed to receive access to safe water annually. This is below the 135 million people that were reached annually during the Water Decade (Scheitenleib, 1993; UNDP, 1994).
- the assumption that urbanisation rates will be constant after 2010. This is important for the costed technology mix.
- an extrapolation of the historical time series based on the review by Cleighs (1993) and the international reports (World Bank, 1993; WHO, 1995).

**Service development.** The estimates for the scenarios on total health service expenditure are based on a logarithmic function of GNP per capita and the percentage of GNP devoted to the health service per capita (chapter 3).

**Human development index.** An overall index of the general socio-economic level is the human development index (HDI), which we computed to summarize some of the input scenarios. This is done as described by the UNDP in the Human Development Report for 1994. This index combines health risk parameters (GNP, literacy) with an impact parameter (life expectancy) without accounting for the "input-output" relationship. Limitations of this index are that it is relative insensitive and it only slowly changes over time because of the contribution of three factors. An income level below $200 is used in the scaling as a cut-off point: below it the GNP contribution to the index becomes zero.

### 4.4. SCENARIOS FOR INDIA, MEXICO & THE NETHERLANDS

The case studies show each a characteristic pattern of health determinants in the past and in the future. This pattern determines, as postulated, the largest part of the changes in disease occurrence and related mortality decline. To be able to do this, we had to make a number of model adaptations of the generic structure. The first adaptation was related to the start values of population, determinants and disease states. For each of the cases the initial values have been adapted based on the above presented historical input scenarios and available additional data. If not available, they were estimated by an initialization run for eight hundred years to calculate the equilibrium values, typically for the early transition phase. Next, some adaptations were made in
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the disease model, although less extensive. We had to include a malnourished fraction among those born to fit the number of perinatal deaths to the empirical figures. The consequence was an overestimation of the simulated number of life births as compared to the empirical figures. This is very likely due to an underreporting of perinatal deaths. The fraction malnourished disappears later in the scenarios as malnutrition disappears and perinatal mortality lowers as a consequence of economic growth. The timing of technology was adapted to reflect the observed onset of medical technology by changing the effectiveness function.

We have included some structural model adaptations in the generic model. The other adaptations are basically value adaptations, including the timing of the introduction of technology and modern family planning. These do not influence our postulate on the generic nature of modelling disease occurrence in stages of the health transition and the modelling framework.

<table>
<thead>
<tr>
<th>Health determinant</th>
<th>input scenario by calendar year</th>
<th>annual change (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. India</strong></td>
<td>year</td>
<td>1990 2025 2050 2025 2050</td>
<td></td>
</tr>
<tr>
<td>GNP (10^12 US$1990)</td>
<td>0.3    0.7  3.7  4.3  3.8</td>
<td>WB, 1991</td>
<td></td>
</tr>
<tr>
<td>GNP per capita (10^3 US$1990)</td>
<td>0.3    1.0  1.8  3.0  3.0</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Percentage in poverty</td>
<td>43 28  14  -1.2  -2.7</td>
<td>function estimate</td>
<td></td>
</tr>
<tr>
<td>Population in poverty (10^6)</td>
<td>365 400  270  3.0  -1.5</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Health expenditure (% GNP)</td>
<td>3.7    3.8  3.9  0.0  0.1</td>
<td>OECD, 1995</td>
<td></td>
</tr>
<tr>
<td>Food per capita (10^3 kcal/day)</td>
<td>2.2    2.6  2.9  0.5  0.5</td>
<td>Rosegrant, 1995</td>
<td></td>
</tr>
<tr>
<td>Safe water and sanitation (%)</td>
<td>56 100  100  1.6  0.0</td>
<td>Majumdar, 1994</td>
<td></td>
</tr>
<tr>
<td>Population (10^6)</td>
<td>840 1,400  1,900  1.3  1.3</td>
<td>UN, 1993</td>
<td></td>
</tr>
<tr>
<td><strong>b. México</strong></td>
<td>year</td>
<td>1990 2025 2050 2025 2050</td>
<td></td>
</tr>
<tr>
<td>GNP (10^12 US$1990)</td>
<td>0.2    0.8  2.0  3.2  2.8</td>
<td>WB, 1991</td>
<td></td>
</tr>
<tr>
<td>GNP per capita (10^3 US$1990)</td>
<td>3.0    5.5  11  1.7  2.2</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Percentage in poverty</td>
<td>17 50  0.1  -0.4  -0.1</td>
<td>function estimate</td>
<td></td>
</tr>
<tr>
<td>Population in poverty (10^6)</td>
<td>15  6.5  0.2  -0.3  -0.4</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Health expenditure (% GNP)</td>
<td>4.0    5.0  7.1  0.2  0.4</td>
<td>OECD, 1995</td>
<td></td>
</tr>
<tr>
<td>Food per capita (10^3 kcal/day)</td>
<td>2.7    3.2  3.5  0.4  0.4</td>
<td>Rosegrant, 1995</td>
<td></td>
</tr>
<tr>
<td>Safe water and sanitation (%)</td>
<td>71 100  100  1.0  0.0</td>
<td>Majumdar, 1994</td>
<td></td>
</tr>
<tr>
<td>Population (10^6)</td>
<td>83 122  160  1.1  1.1</td>
<td>UN, 1991</td>
<td></td>
</tr>
<tr>
<td><strong>c. The Netherlands</strong></td>
<td>year</td>
<td>1860 1900 1950 1990 1950 1990</td>
<td></td>
</tr>
<tr>
<td>GNP (10^12 US$1990)</td>
<td>0.0005 0.001 0.01 0.3 3.3 9.0</td>
<td>Stuijvenberg, 1970</td>
<td></td>
</tr>
<tr>
<td>GNP per capita (10^3 US$1990)</td>
<td>0.15  0.2  0.9  19 2.0  8.0</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Percentage in poverty</td>
<td>49 48  0.1  0.0  -2.4  -2.0</td>
<td>function estimate</td>
<td></td>
</tr>
<tr>
<td>Population in poverty (10^6)</td>
<td>1.5  2.4  0.1  0.0  -5.1  -0.1</td>
<td>ibid</td>
<td></td>
</tr>
<tr>
<td>Health expenditure (% GNP)</td>
<td>0.1  0.1  3.9  8.2  4.0  1.8</td>
<td>OECD, 1995</td>
<td></td>
</tr>
<tr>
<td>Food per capita (10^3 kcal/day)</td>
<td>2.2    3.0  3.2  3.5  0.2  0.2</td>
<td>Jobse-Putten, 1995</td>
<td></td>
</tr>
<tr>
<td>Safe water and sanitation (%)</td>
<td>8.0  42  95  100  2.5  0.1</td>
<td>Zon, 1986</td>
<td></td>
</tr>
<tr>
<td>Population (10^6)</td>
<td>3.0  5.1  10  15  1.3  1.0</td>
<td>CBS, 1990</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.2. Health determinant input scenarios by calendar year for India, Mexico and The Netherlands. Other sources on India: Hutter et al. 1995; Arnold, 1993; Resource Analysis, 1994; TARU, 1993; on Mexico: Kunitz, 1993; Bobadilla, 1993; Vianen et al., 1996; Nicholas et al, 1993; on the historical Dutch scenarios are van Deursen (1994) on literacy and Houwaart (1991) on health care development.
The scenarios on the health determinants for the three countries are listed in the Table 4.2 below. The estimated changes in poverty level are shown in Figure 4.4. In spite of the optimistic economic scenarios one can observe that the absolute number of poor in India tend to remain at the same level for some time. In the Mexican case, one can observe an early economic growth and general human development.

The scenario set for the Netherlands is based on estimated historical figures. The historic time series for GNP is based on a Dutch publication (Stuijvenberg, 1970) and the literacy data on a report by van Deursen (1994). Figure 4.2 shows the changes in GNP, calculated in US$ on a purchasing power parity basis (World Bank, 1992). The number of poor decreases faster than in the Mexican and Indian scenario as the result of the speedy economic development and the slower increase in population. Figure 4.3 shows the time series on food availability by Jobse (1995). The average diet by the middle of the last century consisted of potatoes and some bread. During the so-called dark European decades of 1840-1860, there were a number of famines in Europe and in the Netherlands. The Netherlands show a slow overall increase in food availability after that period but diversity is lacking. The calculation of available
kilocalories per day has been made in a standard manner: This means that 1 kilogram of meat is taken as the equivalent of 7 kg of vegetables and 1 kilogram vegetable as the equivalent of 3500 kilocalories (FAO, 1992). The outcome of the calculation for the 1840-1960 period is comparable to those found for England (2000-2200 kcal/cap/day).

Figure 4.4. Population below poverty level in relative figures (rectangles) and absolute numbers (triangles).
as calculated by Fogel in a Swedish Academy of Science paper (Kiessling and Landberg, 1994). The complete food scenario (Figure 4.5) includes a shortage of food during the end of the Second World War. This situation is comparable to the levels of one century earlier for both kilocalories per capita available as the reached level of life expectancy at birth (CBS, 1990; Tabeau, 1995). The estimations of water access and sanitation coverage are based on van Zon (1986) and Houwaart (1991). In 1860, only Amsterdam had a drinking water supply and suggestively lower mortality rates (van Loghum, 1953). In most towns there was a door-to-door bucket collection system. During the second half of the 19th century the Commission on Drinking Water (1875) succeeded to mobilise policy makers to make relatively huge investments in the water and sanitation infrastructure. By the year 1890 there was coverage of 51 municipalities. The historical scenarios for India and Mexico are based on empirical national estimates based on local literature and reports. The future scenarios for the countries are mostly based on World Bank scenarios (WB, 1993). The food scenarios are by the Food and Agriculture Organisation. One can see that the optimistic scenario for Mexico after 2000 leads to a rapid decline of people living below the poverty line. The moderate scenario for India results in a very slow decline of poverty with a persistent absolute number of more than 300 millions of people still under the poverty line. First, the historical demographic figures, such as crude death rate and life expectancy have been calibrated. In the case of Mexico the figures in Basch (1994) on the change in mortality causes between 1950 and 1990 have been used (see also Fundacion, 1994). For India, only a limited calibration was possible, as disease-specific figures were available for only a decade.

4.5. RESULTS

Figure 4.5 shows the overall results for three case studies, under the health determinant scenarios based on assumptions regarding water availability, food security and human development and health services. The Human Development Index (HDI) is a combined figure for life expectancy, GNP and literacy levels. Looking closer at the changes in the human development index one can observe the interplay between population changes and socio-economic development. The HDI for Mexico shows an early rise as the consequence of economic growth and increase in literacy. Despite of optimistic economic scenarios for India potential changes in HDI are lower as a result of population increase. Still there is a rise in HDI as the result of increases in literacy and life expectancy. The early rise in HDI for the Netherlands is mainly caused by an increase in literacy and an increase in life expectancy as the result of better nutritional status and improved sanitary conditions. Economic growth in Mexico and in the Netherlands allows for considerable growth in service expenditure per capita, while, again this is much lower for India.
4.5.1. CHANGES IN LIFE EXPECTANCY AND POPULATION

In the Figure 4.6 the calibrated results for all three case studies are depicted for life expectancy and population size. They show the different patterns of population change and the different pathways through the health transition. Changes for India are huge and include a gradual fertility decline and life expectancy increase. Mexico shows a very rapid increase in population size, also historically (already a 700% in 1990). This is a result of a late onset of the fertility decline (since 1972) in spite of an early economic growth (since 1940) combined with an early rise in life expectancy at the start of this century. Population policy has been absent most of the time and, if present, rather pronatalist for socio-cultural reasons, until recently (Vianen et al., 1995). In the long run, as the result of a speeded-up fertility transition the projected total number of people at the end of the last century is lower than projected by trend extrapolation. Another additional factor is that the present model has not been corrected for the annual net migration figures. This would make the empirical figures go up or down to a limited
extend. The entry of the health transition is due to the already moderate levels of social development reflected in literacy rates in general and for women and the higher economic status of a large proportion of the population (Figure 4.4). The empirical fertility level for the Netherlands remains, nevertheless, rather high as compared to other European countries and as compared to the projected increase for India. In the case of Mexico, the decrease in mortality combined with the high fertility leads to population increase that is twice the increase in the Netherlands and India.

4.5.2. BURDEN OF DISEASE BY HEALTH DETERMINANTS

Figure 4.7. depicts the computed health expectancies (DALE) for the three case populations. Here, the disease burden is expressed in lost years in disability-weighted life expectancy, by the main health determinant clusters as outlined in the previous chapter. The three clusters used in the figure are 1. life-style i.e. smoking and
hypertension, 2. environment-related causes (lack of safe water, lack of sufficient food, malaria presence, and other environmental conditions) combined with conditions of low SES status, and 3. low SES status, or poverty, only.

**Disease burden for India.** The changes in health expectancy depicted in Figure 4.7 are computed in comparison to an assumed upper limit of 81 years. Early in the present century the lost life years reflects the level of life expectancy as the total lost DALYs are determined by perinatal and early childhood mortality. Years lost because of low quality environmental conditions in combination with low SES status are many. India’s transition is starting only in the 1950s at the onset of the economic growth (in relative figures) but also, slightly later, the onset of the Green Revolution. As food and water supply improve, the lost life years among persons living in low SES conditions only increase as a result of substitution of health risks. The loss of life years attributable to life style only slowly increases as these appear at older ages. One can observe (Figure 4.7. and 4.10) that the modelled transition for India is protracted and results in a double burden of disease: both from infections and chronic diseases. Presently there are still a substantial number of deaths related to the environment-low SES status-infections complex (Resource Analysis, 1994; Hutter, 1995).

**Disease burden for Mexico** The scenarios are optimistic regarding the improvements in sanitary conditions and food availability. Hence, the model demonstrates the shift from health loss because of lack of hygiene, malnutrition combined with low SES status to a low SES status only. There is an additional shift to health loss due to life style factors as the consequence of increased economic development and higher income status. This excess of life years lost is not countered by effects of modern curative services, as, in contrast, has been the case in the Netherlands. Here, typically for Mexico, one can observe (Figure 4.7.) that the modelled transition results in a double burden of disease: both from infections and chronic diseases. Throughout the 20th century, as is shown in other studies on Mexico, there is still a 15-25 years of life lost that can be shown in the computed life expectancy and also expressed as DALYs lost per thousand.

**Disease burden for The Netherlands.** At the impact level the model demonstrates health loss due to lack of hygiene, malnutrition combined with low SES status during the 19th century. This improvement resulted in the onset of the second stage of the health transition in a population growth. Low SES estimations remain high and loss of life years in this group remains high, also at total population level. There is a considerable gain in life years during the beginning of the present century (RIVM, 1995). After the Second World War the loss due to life-style factors dominates but flattens. Inevitably, the figures after this period are less precise but comparable to results from others (Ginneken, 1994). For a better analysis of this period more detailed models are needed.
Figure 4.7. Health expectancy and loss by health determinant category for India, Mexico, and The Netherlands (UNEP, 1997).
4.5.3. THE CONTRIBUTION OF HEALTH SERVICES

We explored the increased disease survival attributable to health services, both curative and preventive, only for the Netherlands. In this country the level of expenditure and the quality of the services are assumed to be sufficient enough to have a health impact at the population level (Mackenbach, 1988). By 1950 the two broad health determinants, malnutrition and low SES, are not contributing to health loss anymore. It is explored how the health gain since 1950 can be attributed to health services development (Treurniet, 1994). Figure 4.8 shows the effect of total health service expenditure, both prevention and cure (over 90% of the budget) on life expectancy. In this run a zero health expenditure scenario is simulated. This results in a change to the worst values for all the remaining health risks, including those for disease survival. As a result life expectancy is reduced considerably (about 12-15 years) and is even decreasing as the effect of another health determinant i.e. the increase in smoking prevalence among men and women.

4.6. DISCUSSION: MULTIPLE ROADS TO HEALTH

A different pattern of health determinants and disease leads to a different pattern of disease and mortality in populations. Below this 'phenotype' other health risks may or may not be present and play a role. Figure 4.9 shows a model experiment to illustrate competition and substitution of health risks, using the input and output data for The Netherlands. The figure on top shows two hypothetical safe water interventions and the figure below shows changes in health expectancy and attributable losses due to health determinants (see 4.5.2). The input scenario for access to safe water has been changed dramatically, twice, during the period of mortality decline. The early intervention with a
large increase in safe water access results in corresponding increase in weighted life expectancy. At the same time there is a shift in health risks that causes loss of life years. In the presence of safe water supply, the socio-economic status of the same sub population involved remains unchanged.

Figure 4.9. Upper graph shows two hypothetical scenarios for water-access campaigns and lower graph shows the shifting effect of competing, health risks (Dutch model version).

Consequently, for this population group this will have two effects shown in the figure: 1) inadequate water handling is still causing loss of health and 2) there is a no loss of healthy years due to life style related determinants. Next, the second simulated sudden complete increase in safe water access shows less increase in weighted life expectancy,
as there is less to be gained. The concomitant increase in food availability limits also environment-related loss of years.

The summary output for the three case studies are shown in Figure 4.10. It shows a comparison of the changes in socio-economic development, summarized by the human development index (HDI) and the changes at impact level (population size and life expectancy) for the three countries. One observes differences in timing and speed of the changes for each of the figures. Changes in HDI and life expectancy in the first stage of the transition run parallel for Mexico and India while for The Netherlands the HDI lags behind the increase in life expectancy. India and Mexico show a slowly
increasing *HDI* and life expectancy and a huge increase in population. In India this continues and the population is expected to increase even more. In Mexico, the huge population growth slows down as the *HDI* improves further. In The Netherlands, changes in life expectancy and population increase have been observed while the *HDI* remains low due to low economic growth. In the second stage, when population growth is not paralleled with an increase in *HDI*, life expectancy improvement may nevertheless lag behind (see India). A later rise in *HDI* does have less effect (Mexico and the Netherlands). In the case of Mexico, one can observe slowly converging tendencies and a stabilization of the population. A similar pattern one has observed for the Netherlands. In the latter, health gain has been achieved mainly because of factors not related to the *HDI*. The general level of this index remains low for a long time but still there is stabilization.

Studying the changes in the various health determinants for the three countries (*Figure 43.7*), again one can observe that different health determinants lead to additional health gains. For life expectancy, Mexico and The Netherlands show a gradual increase starting at the beginning of this century and even earlier. Socio-economic and environmental improvements run parallel for Mexico (*Table 4.2b*). In the Netherlands environmental improvements dominate early on, while low SES status in the Netherlands disappears rapidly by the end of the war due to economic growth. For both countries life style factors become a leading cause of loss of health. Only for the Netherlands there is a further increase due to the effect of preventive and curative services. For India our calculations show a rapid retrieval of life years lost from environmental causes and slow improvement in SES early last century. In the seventies and eighties there is an improved availability of food per capita that contributes during this period to the increase in life expectancy. There is a projected continuous loss of life years by people living in low economic status from 1950 onwards and also in future. Life style factors initially play a lesser role.

### 4.7. CONCLUSIONS

Based on official scenarios, the generic model framework shows that it can account for competing, multiple health determinants and multiple disease describing historical mortality declines in the three countries. In the Netherlands, literacy and increases in socio-economic status lead to considerable high health levels even without the interventions related to modern health care. With the introduction of modern care, life expectancy increased even more, but with diminishing returns. In Mexico, simultaneous increases in SES and access to modern health care lead to a fast increase in health levels. In India all improvements in health determinants seem to be there but increases are at a slower rate. The two model experiments show the net estimates of the contribution of health services as a function of the level of other health determinants.

The improvements in health determinants have three distinct features: 1) the substitution and competition of health risks and diseases causing a certain inertia in the improvement of health, 2) the prevention of cohorts becoming ill and, 3) increased survival after entering disease states. There are no unique solutions in the
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quantification of the role of health determinants in the mortality transition for specified populations. The contribution of each determinant is always depending on the level of other health determinants. Each population is bound to follow its own path in the transition defined by the country-specific pattern of health determinants. Time series of historical disease-specific mortality rates should be used for further calibration and validation of model outcomes. This will result in a reduction of uncertainties in parameter values. Historical national data series in a number of European countries will be suitable. More recent time series for Sub-Saharan countries might also be suitable for additional model applications. Many more applications are possible, especially for the design of optimal strategies in the improvement of health determinants.
REFERENCES

CHAPTER 5

LATE TRANSITIONAL MORTALITY CHANGE: STROKE

5.1. SUMMARY

Introduction This chapter describes an example of a disease-specific multi-state model to estimate mortality decline. Trends in stroke incidence and survival determine changes in stroke both morbidity and mortality. It examines the extent of the incidence decline and survival improvement in the Netherlands from 1979-1989 and it projects future changes in stroke morbidity over the period 1985-2005 when the country's population will be aging. Next, it evaluates the health effects and costs of a number of stroke interventions.

Methods A multi-state model is used, which combines existing data and describes stroke epidemiology in the Netherlands. Based on the clinical course of stroke, the model describes historical national age- and gender-specific hospital admission and mortality rates for stroke.

Results: There is evidence of a continuing incidence decline. The most plausible rate of change is an annual decline of -1.9% (range: -1.7; -2.1) for men and -2.4% (range: -2.3; -2.8) for women. Projecting a constant mortality decline, the model shows a 35% decrease of the stroke incidence rate over a period of twenty years. Prevalence rates for major stroke will decline among the younger age groups. They will increase among the oldest due to increased survival in the latter. In absolute numbers, this results in an 18% decrease of acute stroke episodes and an 11% increase of major stroke cases.

Conclusion The increase in survival cannot fully explain the observed mortality decline and, therefore, a concomitant incidence decline has to be assumed. Aging of the population partially outweighs the effect of an incidence decline on the total burden of stroke. Increase in cardiovascular survival leads to a further increase in major stroke prevalence among the oldest.
5.2. INTRODUCTION

The dynamics of stroke morbidity and mortality are of major interest for clinicians as well as for epidemiologists and health policy makers. A changing stroke epidemiology results from changes in incidence and survival. The balance between these trends determines the numbers of short and long-term stroke survivors within a population. Recently, the debate on the relative contribution of trends in incidence and survival to stroke mortality decline has intensified, complicated by different study methods and inconsistent results (Casper et al., 1992; Harmsen et al, 1992; McGovern et al., 1992; Modan and Wagner, 1992).

In the Netherlands as well as in the USA, stroke mortality has been declining for all age groups since the early sixties (Casper et al., 1992; McGovern et al., 1992; Modan and Wagner, 1992; Bonita et al., 1990; Central Bureau of Statistics, 1985). In the Netherlands, the age-adjusted decline from 1979-1989 has been a constant 3.1 % per year for men and 4.0% for women, while in the USA mortality decline has been 5.7% and 5.2%, respectively (McGovern et al., 1992; Central Bureau of Statistics, 1985). An incidence decline is also observed (Broderick et al, 1989; Kotila, 1988; Terent, 1989), ascribed to better hypertension control and a decline in smoking prevalence (Broderick et al, 1989; Kotila, 1988; Tuomilehto et al., 1991). Observed incidence trends are confounded by the introduction of computerised tomography, improving the specificity of the diagnosis but also increasing case finding. Declines in short and long term case fatality have been documented for the last decades (Broderick et al, 1989; Terent, 1989; Sacco et al., 1982; Howard et al., 1989; Klag et al., 1989). It is explained mainly by a better prognosis after intra-cerebral haemorrhage, by increased hypertension control (Broderick et al, 1989; Tuomilehto et al., 1991), and by a better prevention and treatment of complications, especially of cardiac disease. However, the observed mortality decline has started long ago and cannot be fully accounted for by observed changes in risk factors. Most likely, both incidence and case-fatality decline will remain largely unexplained (McGovern et al., 1992; Klag et al., 1989).

This chapter determines the most plausible range of incidence and fatality decline that explains the impressive observed reduction in stroke mortality in the Netherlands by means of a multi-state model (Central Bureau of Statistics, 1985). Next, it shows the projected future changes in stroke incidence and prevalence using the calculated trend values.

5.3. MODEL DESCRIPTION AND VALIDATION

Changes in stroke occurrence and stroke mortality are determined by changes in stroke incidence, survival, recovery, recurrence, and mortality from other diseases. Given this complexity, a mathematical model is indispensable (Weinstein, 1989). We developed a multi-state model that is based on the clinical course of stroke (Figure 5.1). Combining data from various sources, the model describes the epidemiology of stroke in the Netherlands. The basic principle of the multi-state model for stroke is that patients move from one particular state to another after experiencing a particular
The likelihood to move from one state to another, a transition probability, is assumed to be independent from the preceding states or events and depends only on the current state defined by disease stage, age and gender during the event (Markov assumption). All probabilities are age and gender specific. There are five-year age groups ranging from 25 years to 90 and over. Risk of death from other causes is accounted for in all states. The model is combined with national population projections to calculate national estimates (Central Bureau of Statistics, 1985). During computation, the model annually generates first incident cases. These enter the respective states within the stroke specific component and follow the various flows with the model. Simultaneously, the model also annually updates all existing prevalent states for recurrences and their consequences.

![Diagram](image-url)  
*Figure 5.1. Diagram presenting the multi-state model for stroke. Major stroke results in severe disability. The boxes indicate health states; the circles indicate events and the arrows the transitions. Recurrent stroke indicates second or more stroke events.*
Within the stroke disease component of the model two events can occur: a transient ischemic attack (TIA) or a stroke, both defined as in the Oxford Community Stroke Project (OCSP; Bamford et al., 1988; Dennis et al., 1989). We distinguished different states for the first year and for all subsequent years together. The flows in the model during the first year and the subsequent years are almost identical, except for recovery. In a TIA state the patient has an increased risk of stroke. After the first year, patients with a history of a TIA enter the "subsequent years" state and run a lower stroke risk. This latter risk is the same for the rest of their lives. A separate first month state after a first stroke allows for the acute phase with a high risk of disability and death. After a first stroke patients enter this state. Patients surviving the first month are left either with a minor or major stroke as defined by a Rankin grade 0-2 and 3-5 (van Swieten et al., 1988), respectively, and are divided up between the two separate states. Patients with a history of stroke run a risk of recurrence. If this occurs, there is an excess risk of dying or having a major stroke. In the first year state for major stroke, some patients recover, defined by Rankin grade 0-2. The recovered patients enter the minor stroke state. The remaining fraction moves to the major stroke state for all subsequent years. Also in both late stroke states the risk are lower and the same for the rest of the years alive. In both major stroke states a patient suffers a delayed death due to a first and disabling stroke.

One model assumption is that in the acute phase almost all deaths can be contributed to the first stroke and only a few to the other causes of death. In this phase, the risk of recurrence and the excess risk of death from heart disease are not accounted for due to an absence of recorded data. Also, a single state for all subsequent years together implies that the recurrence risk in subsequent years state is the same for all following years. This is supported by recent Dutch data (Dutch TIA Trial Study Group, 1991). Next, we do not distinguish strokes caused by intra-cerebral haemorrhage and by cerebral infarction. From a patient-based view, these are different. At the aggregated population level a distinction is less useful as trombotic infarctions make up more than 80% of all the stroke case (Bamford et al., 1988; Herman et al., 1982). Moreover, the survival after a haemorrhagic stroke is reaching the level of survival after an infarction due to improved prognosis and due to increased detection of smaller and less harmful bleedings (Giroud et al., 1991).

**Input data: epidemiology**

The origin of the crude epidemiological data used to calculate the base-line input is summarised in Table 5.1. We have calculated the age-specific transition probabilities using the results of Dutch population-based studies, if available. If incomplete, they have been used to check selected comparable figures of other Caucasian populations as listed in the table. Relative risks are used when comparing risks for one patient category with another. Ratios are used as transition probabilities without further calculations. The choice of measure depends on the way the data have been made available.

The risk of a first TIA is calculated using the incidence figures from the OCSP (Dennis et al., 1989). Age-specific probabilities are calculated by exponential interpolation and are comparable to data from Dutch primary care practices (NUHI;
vanden Hoogen et al, 1985) and also the Rochester study (Dennis et al., 1990). The relative risks of stroke after a first TIA reported by the OCSP have been interpolated. They are multiplied by the population risks from the Tilburg Epidemiological Study of Stroke (TESS) and the Oxford Project to calculate age-specific absolute stroke risks after a TIA. (Bamford et al., 1988; Herman et al., 1982).

Table 5.1. Crude literature data used to calculate base-line transition probabilities by age and sex for the stroke model and the resulting transition probabilities for one patients group (male, 70-74 years).

<table>
<thead>
<tr>
<th>Event</th>
<th>Crude data Measure</th>
<th>Probability 70-74 years</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>First TIA</td>
<td>Rate 0.42/10³</td>
<td>0.0037/0.0026</td>
<td>Hoogen, 1985; Bamford, 1988</td>
</tr>
<tr>
<td>First stroke</td>
<td>Rate 1.62/10³</td>
<td>0.0112/0.010</td>
<td>Herman, 1982; Bamford, 1988</td>
</tr>
<tr>
<td>Death from first stroke</td>
<td>Ratio 0.20</td>
<td>0.21/0.21</td>
<td>Ibid</td>
</tr>
<tr>
<td>Major disability after stroke</td>
<td>Ratio 0.39</td>
<td>0.39</td>
<td>Bamford, 1988</td>
</tr>
<tr>
<td>Recovery from major stroke</td>
<td>Ratio 0.76</td>
<td>0.22</td>
<td>Meer &amp; Smith, 1990; Bonita, 1988</td>
</tr>
<tr>
<td>Recurrent after minor stroke first year &lt;75 years</td>
<td>RR 13.2</td>
<td>0.09/0.07</td>
<td>Dutch TIA Trial, 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recurrent years</td>
<td>5.0</td>
<td>0.05/0.04</td>
<td></td>
</tr>
<tr>
<td>Late death from major stroke</td>
<td>Ratio 0.17/0.42</td>
<td>0.15/0.11</td>
<td>CBS, 1985; Howard, 1986 &amp; 1991</td>
</tr>
<tr>
<td></td>
<td>MHR* 1.261</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of cardiac disease after TIA / or stroke</td>
<td>RR 3.2</td>
<td>0.038/0.025</td>
<td>Dutch TIA Trial, 1991; Howard, 1986 &amp; 1991</td>
</tr>
<tr>
<td></td>
<td>MHR‡ 0.665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of cardiac disease after major stroke</td>
<td>RR $ 1.57</td>
<td>0.06/0.04</td>
<td>Howard, 1986 &amp; 1991</td>
</tr>
</tbody>
</table>

Probabilities of a first stroke are calculated by averaging the results of the incidence studies by the OCSP and the TESS that have produced similar figures (Bamford et al., 1988; Herman et al., 1982). As the TESS included fewer age groups, the results of both studies are combined to have reliable incidence figures for as many age groups as possible. Results are consistent with the NUHI data (vanden Hoogen 1985). Age-adjusted all stroke case-fatality rates from the TESS study have been corrected for recurrences by assuming a twice as high risk of a stroke death. The resulting case-fatality ratios of the OCSP and TESS are nearly identical (19% and 20%). The probability of residual major disability after one month is assumed to be constant for age and gender (Bonita and Beaglehole, 1988). The recurrence risk for minor stroke patients is assumed the same as the first stroke risk for TIA patients. The ratio of the risk of dying after a recurrence versus the risk after a first ever stroke is 1.5 (Howard, et al, 1986). For the risk of a major stroke after a recurrence, the same ratio is used. Recurrence risk in the subsequent years state after a minor stroke is estimated half the first year risk (Dutch TIA Trial Group, 1991) with the same risk of dying and of major stroke, given the recurrence, as during the first year (Howard et al., 1991). The probability of recovery from major stroke has been calculated by age group and is the same for both sexes (Herman et al., 1982). In agreement with various studies
Stroke mortality

(Terent, 1989; Herman et al., 1982; Howard et al., 1986) recurrence risk and subsequent death after major stroke has been estimated by doubling the hazard ratio of the same parameter as found by Howard (1986) for the minor stroke group. Late stroke mortality during subsequent years is half the risk in the first-year state. The recurrence risk in the subsequent years state after a disabling stroke is half the first year risk (Kotila, 1988; Tuomilehto et al., 1991) as assumed for minor stroke.

The excess age-specific risk of death from ischemic heart disease (ICD 410-414) in the prevalent states has been calculated by multiplying the hazard ratios for cardiac death (Bonita and Beaglehole, 1988; Howard et al., 1986) with the age-specific risk of death from ischemic heart disease for the general Dutch population (CBS, 1986).

Risk of death from other causes is calculated using the all causes death rates from the national death registry corrected for the stroke related figures (International Classification of Diseases (ICD) codes 430-438).

The stroke disease model in combination with the demographic data and projections describes the stroke epidemiology for the Dutch population in steady state. It has been presented with fixed transition probabilities. The model estimates stroke prevalence for the baseline year (Figure 5.4) after assuming the same probabilities during the preceding years.

The stroke model produces national estimates regarding the stroke epidemiology including first stroke incidence, stroke recurrences as well as stroke mortality and prevalence. Figure 5.2 shows the model outcome regarding national stroke hospital rates, including both fatal and non-fatal cases, and national stroke mortality rates for the 1985 baseline year. There is a good fit for the age groups up to 80 years between model outcomes and the national data of the same year (CBS, 1986; van der Meer and Smith, 1990): the $X^2$ for men is 8.10 and 6.37, respectively and for women the $X^2$ is 6.21 and 8.15 (all $P$ values are larger than 0.5, d.f. = 11). These chi-square values support the validity of the model. The national admission rate (Meer and Smith, 1990) for the 85 year old and over from the hospital registry is lower than the model admission rate, as the latter refers to the age group 85-89 only. The lower model stroke deaths rates of the same age group is most probably due to an over-registration of stroke deaths for this age group in general practice and/or a possible under-registration of incidence in the OCSP and TESS.

The external validation of the stroke model for the Dutch population consists of comparing calculated age- and sex-specific figures on stroke events and mortality to the national empirical figures on acute hospital admissions and stroke mortality. As this study is on long-term survival and costs, we validated calculated major stroke prevalence against nursing home data.

**Input data: epidemiologic time trends**

The model allows for age-specific time trends for all the transition probabilities depicted in Figure 5.1. This allows for plausible projections over longer periods. The value of these trends is calculated by time series analysis of available figures from comparable populations. A trend is defined as the annual percent change, which
means an exponential change. To calculate this kind of trend, first, a log-transformation is applied. The regression line, through the log-transformed figures of each time interval is determined by least squares fit. The regression coefficient, or slope, of this line, is the annual percent change of the time series figures (Bonita et al., 1990). During computation, two sets of trends are used. One set consists of all

Figure 5.2. External validation of stroke model output: age-specific hospital admission rates (upper curves) and death rates (lower curves) for all strokes, in The Netherlands, 1985 according to national registries (CBS, 1985; Information Centre for Health Care, 1990) (markers) and as calculated by the model (lines). Rates are in 0/000. Model hospital admission rates are based on the model events rates for all strokes together multiplied by age-specific chances of admission (Information Centre for Health Care, 1990).
"attack" parameters: the risks of a TIA, first stroke, or recurrence. The other set includes all parameters regarding acute and late case-fatality of stroke accounting for the decreasing severity of stroke. This study focuses on the first stroke incidence and case-fatality trends.

These trends in transition probabilities are not very well documented. The Rochester study\(^7\) is the only study that produces age and gender specific data on the secular changes both in stroke incidence and fatality. We applied the Rochester incidence and case-fatality trends to the respective "attack" and "case-fatality" sets of trends within the model. This can be done as the Dutch incidence figures for TIA and stroke as well as case-fatality ratios over a single two-year period (vanden Hoogen et al., 1985; Herman et al., 1986) agree with comparable Rochester data. We ignored the recent, most likely temporary, incidence increase for Rochester caused by increased case finding because of the introduction of computerised tomography\(^7\). Trends in the two remaining transition probabilities, the risk of major stroke after stroke, and the chance of recovery from a major stroke are not known and are assumed constant. The application of the Rochester incidence and survival trends appear to reproduce almost identical sex-specific mortality trends as observed in the Netherlands from 1979 to 1989 (Bonita et al., 1990; CBS, 1985) (see table 5.2). This seems logical, as both populations are mainly Caucasian and comparable in most other aspects. Other combinations of trend values for incidence and case-fatality (Kotila, 1988; Howard et al., 1989; CBS, 1986; Garraway et al., 1983; Malgren, 1987), however, can also account for the observed mortality decline. The difficulty is that trend values are reported mostly separately from each other and without corresponding overall mortality trend.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>incidence (annual trend)</th>
<th>case-fatality (annual trend)</th>
<th>X²</th>
<th>A*</th>
<th>incidence (annual trend)</th>
<th>case-fatality (annual trend)</th>
<th>X²</th>
<th>A*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper</td>
<td>1.7</td>
<td>-1.7</td>
<td>1.02</td>
<td>&gt;0.5</td>
<td>-2.3</td>
<td>-1.7</td>
<td>1.08</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Rochester</td>
<td>-1.9</td>
<td>-1.3</td>
<td>0.46</td>
<td>&gt;0.5</td>
<td>-2.4</td>
<td>-1.3</td>
<td>0.55</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Lower</td>
<td>-2.1</td>
<td>-1.0</td>
<td>0.71</td>
<td>&gt;0.5</td>
<td>-2.8</td>
<td>-1.0</td>
<td>0.72</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

Table 5.2. Values of annual incidence and case-fatality trends applied in the stroke model as well as the goodness-of-fit of the corresponding model mortality trends with the empirical Dutch national mortality trend for 1979-1989. *Degrees of freedom: 10 (number of age groups-1)*(number of categories-1). † A is a goodness of fit parameter; > 0.5 indicates a good fit.

To solve this we used a two-way sensitivity analysis of incidence and case-fatality trends to determine a plausible range of values (Figure 5.3). In the analysis, for each value of one set of trends we calculated the corresponding value of the other set that, in combination, leads to the same mortality decline. Under the condition of a fixed mortality decline, the incidence and case-fatality trends are inversely proportional. When the incidence rates decrease, the case fatality rates have to increase five times as rapidly to outweigh the decreasing mortality decline. The main reason for this is that the case-fatality after a first stroke is 20%. This inverse relation leads to the iso-mortality lines in the figure. The area above the lines includes those values of trends
Chapter 5

that lead to a larger mortality decline. The area below includes the values that lead to a lesser mortality decline. The range of reported values for case-fatality trends is small (Broderick et al., 1989; Tuomilehto et al., 1991). Consequently, it defines a much more narrow range of values for a possible incidence decline than is reported in the literature.

Figure 5.3. Plot of a two-way sensitivity analysis of two variables: the stroke incidence trend and the case-fatality trend. The iso-mortality lines shown are for Dutch men (3.1%) and women (4.0%) during the period 1979-1989. Rochester trends for men and women are plotted as well as the most extreme values for both trends found in the literature. The plausible range of incidence decline falls within the range of values in the literature (Broderick, 1989; Tuomilehto et al., 1991; Alo, 1986; Malgren, 1987).
The two-way sensitivity analysis determines the plausible range of values for the incidence trend that explains Dutch stroke mortality decline, given the reported survival improvement. Figure 5.4 and Table 5.2 shows that the values for the incidence trend range between 1.7% and 2.1% per year for men, and between 2.3% and 2.8% per year for women. The figure also demonstrates that, if one supposes no incidence decline, an unreported annual improvement of survival of over 5% would be necessary to fit the observed mortality decline. On the other hand, an incidence decline of over 3%, for men, would, likewise, imply an unreported absence of survival improvement or even deterioration. In Table 5.2 the results of a goodness-of-fit test of the model mortality trends and the empirical trend are given. This is for three plausible scenarios: one with the highest case-fatality improvement, one with the lowest case-fatality improvement and a Rochester-like scenario that turns out to be in between these two case-fatality declines. Assuming no incidence decline and the highest known annual case-fatality improvement, the model computes a mortality decline that does not fit to the national figures.

Statistical testing of the results of the computations consists of a comparison of model results with observed national data. A chi-square goodness-of-fit test is used (Kirkwood, 1988; see appendix). An A value above 0.5 we used to indicate a good fit of the computed results and the observed data. The goodness-of-fit of the model for the age-specific stroke mortality rates and stroke admission rates (first and recurrent strokes together) is given as well as of the trends in the model mortality rates.

5.4. RESULTS

Table 5.3 lists the aggregated model results for 1985 and the relative change of output results for year 2005. Here trend values are used assuming a continuing Rochester-like scenario and, hence, continuing mortality decline. All rates are decreasing and there are no major sex differences. As all attack rates, including risk of recurrence, are assumed to decrease, all stroke rates decrease more than first stroke rates. Due to improved survival, the drop in prevalence rates is considerably less. The projected decline in stroke death rate, is the same as during the past twenty year in the Netherlands (CBS, 1985; Bonita, 1990). This has been the basic assumption of this projection.

Resulting prevalence rates for major stroke are given in Figure 5.5 and agree with the population-based rates found in Finland and Rochester (Alo, 1986). The same figure also demonstrates the trend dynamics by a step-wise inclusion of the two "attack" and "case-fatality" sets of trends that are based on the time series analysis of the Rochester data. A decreasing incidence of stroke results in decreasing major stroke prevalence and likewise, not illustrated, minor stroke prevalence. This decreasing effect on prevalence is nearly halved by an increase in survival, especially of major stroke patients and, to a lesser extent, of minor stroke and TIA patients who live longer with the risk of suffering a debilitating stroke. The effect of survival improvement on stroke prevalence increases with age. This results in an increase in stroke prevalence among the higher age groups.
Chapter 5

Figure 5.5 shows the projected age-specific absolute changes in prevalence rate over the twenty-year period. The decrease of age specific stroke mortality is largest for persons in their late sixties and seventies (CBS, 1985; Bonita, 1990). Case-fatality decline within these age groups has been limited also (Bonita, 1990), so for these

Figure 5.4. Major stroke prevalence rate for 1985 and 2005, by age and sex per 100,000. For 2005, the two runs are shown. During the first run, only the Rochester incidence trend (a decline) is applied to all "attack" parameters. During the second run, the Rochester case-fatality trend (also a decline) on all stroke case-fatality parameters is added.
Figure 5.5. Computed absolute difference in stroke prevalence rate in The Netherlands for 1985-2005 by age and sex (per 100,000). The most plausible trends in incidence and case-fatality are assumed i.e. in continuation of a Rochester-like scenario. Upper and lower limits have been calculated using the extreme values of the range of plausible incidence and case-fatality trends (see sensitivity analysis in Figure 5.3).

persons a rather large incidence decline has to be assumed. Consequently, stroke morbidity among these groups is decreasing remarkably, for men at a younger age than for women. Later in life, the increase in survival results in a large increase in stroke prevalence, offsetting a relatively small incidence decline. In the figure, an upper and lower limit of the age specific prevalence changes is given. These limits are determined by the extreme values of the plausible ranges for incidence decline and
case-fatality decline as reported in Figure 5.4. A smaller incidence decline results in a smaller prevalence decline among the younger patients and a higher morbidity among the older groups. The resulting prevalence changes in these alternative scenarios, again assuming a constant mortality decline, however, are only slightly different.

The effect of the ageing of the post-war baby boom is shown in the shifts in absolute numbers: less of a decline in all stroke cases and even an increase in prevalent cases. The longer life expectancy of Dutch women is reflected in a smaller decrease of first stroke cases and stroke deaths. In general, the incidence decline outweighs the expected increase in absolute numbers of acute stroke episodes with the aging of the post-war generation. Nevertheless, increased survival increases the absolute number of prevalent cases considerably.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First strokes</td>
<td>171</td>
<td>10,600</td>
<td>-35</td>
<td>-16</td>
</tr>
<tr>
<td>All strokes</td>
<td>224</td>
<td>14,000</td>
<td>-37</td>
<td>-19</td>
</tr>
<tr>
<td>First major stroke</td>
<td>67</td>
<td>4,210</td>
<td>-34</td>
<td>-14</td>
</tr>
<tr>
<td>Prevalence major strokes</td>
<td>275</td>
<td>17,300</td>
<td>-15</td>
<td>+11</td>
</tr>
<tr>
<td>Prevalence minor strokes</td>
<td>700</td>
<td>43,900</td>
<td>-12</td>
<td>+15</td>
</tr>
<tr>
<td>Stroke deaths</td>
<td>68</td>
<td>4,170</td>
<td>-46</td>
<td>-30</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First strokes</td>
<td>128</td>
<td>11,200</td>
<td>-36</td>
<td>-9</td>
</tr>
<tr>
<td>All strokes</td>
<td>159</td>
<td>15,000</td>
<td>-38</td>
<td>-17</td>
</tr>
<tr>
<td>First major strokes</td>
<td>46</td>
<td>4,260</td>
<td>-35</td>
<td>-15</td>
</tr>
<tr>
<td>Prevalence major strokes</td>
<td>200</td>
<td>18,400</td>
<td>-17</td>
<td>+8</td>
</tr>
<tr>
<td>Prevalence minor strokes</td>
<td>466</td>
<td>41,300</td>
<td>-13</td>
<td>+11</td>
</tr>
<tr>
<td>Stroke deaths</td>
<td>51</td>
<td>5,110</td>
<td>-45</td>
<td>-23</td>
</tr>
</tbody>
</table>

Table 5.3. Estimated standardised* stroke rates and absolute numbers† of stroke cases in the Netherlands for 1985. Projected future changes for the year 2005 of standardized stroke rates and absolute numbers of stroke cases relative to 1985, assuming continuing Rochester-like trends.

* European standard population; per 100,000.

5.5. DISCUSSION

Downward trends in the occurrence of ischemic heart disease and stroke characterize changes in health within the aging population: reduced disease-specific mortality results in a relatively limited increase in life expectancy but might cause a longer period of severe disability from the same disease (Tsevat et al., 1991). In the case of stroke, the major question is whether declining mortality rates are resulting in a paradoxically, increasing burden of disease, especially among the oldest. The answer depends on whether one supposes mortality and morbidity to be compressed against an alleged fixed biological upper limit to the life span, or whether one supposes a mortality...
decrease in the oldest age groups and a parallel expansion of morbidity. In the former scenario health care provision results in a decrease of morbidity but in the latter it may well result in an increase of chronic morbidity.

Our analysis is based on empirical data from different sources. None of the large population-based studies, or clinical trials have been comprehensive enough to be able to assess the extent of incidence decline and survival improvement in relation to stroke mortality decline. The results show a plausible range of a considerable incidence decline for the Netherlands. As mortality decline in the USA has been much higher (CBS, 1985), incidence decline, most likely, has been higher also. For the Netherlands, consequently, Figure 5.5 confirms a most likely scenario for stroke with a compression of morbidity in the near future, but with an increase of major stroke prevalence among the very old. At a younger age dominant incidence decline results in a decrease in morbidity. For the oldest age groups, however, the decrease in case fatality is larger than the calculated incidence decline and, hence, the resulting mortality decrease is small i.e. about 1% annually (CBS, 1985). At these ages the result is, indeed, a trade-off of stroke mortality for morbidity. The projected changes in morbidity are supported by recent observations: age-adjusted admission rates for stroke are decreasing in the Netherlands (van der Meer and Smith, 1990) and definitely also in the USA among whites (Centers for Disease Control, 1992). In both countries the average age of stroke patients is increasing (van der Meer and Smith, 1990; Centers for Disease Control, 1992). In the Netherlands, the average age of patients admitted to long stay institutions, indicative for the prevalence of major stroke is increasing as well as the average disability score (van der Meer and Smith, 1990). This confirms the changes towards higher major stroke prevalence among higher age groups as reported in Figure 5.5. Similarly the average stay of severely disabled in nursing institutions is increasing and, consequently, the Dutch mortality statistics are showing a parallel increase of late cerebrovascular deaths (ICD code 438) among the oldest. The increased institutionalisation is not explained by social factors, as the intensive home care programme has been expanding the last five years to cope with waiting lists of chronic patients with major stroke.

Next to incidence and survival, stroke morbidity rates are determined by the risk of residual disability after stroke and the chance of recovery. In this respect, some groups are running larger risks after a stroke due to concomitant debilitating diseases like cardiovascular heart disease or due to other risk factors, like hypertension. Ongoing empirical studies, it is hoped, may be able to answer questions regarding stroke trends in these patient groups now that their survival is improving. In addition, empirical studies will have to answer related questions on co-morbidity and disability from other diseases among the aged.

An important question is whether stroke mortality will continue to decline. As most of the mortality decline is unexplained, nobody can be sure about the answer. The stroke model does not answer this question either. In fact, the early nineties have shown a flattening of the mortality decline for all ages. This probably is a period effect, so far unexplained. In its projections we have assumed continuing mortality decline, as this decline has been very constant in the Netherlands. Our model demonstrates the dynamics of stroke morbidity change. Both in the Netherlands and the USA there are still benefits to be gained from large-scale hypertension control (Casper et al., 1992;
McGovern et al., 1992; Gunning-Schepers, 1989; Dyken et al., 1984) and reduction of smoking (Tsevat et al., 1991; Gunning-Schepers, 1989; Dyken et al., 1984). Better intervention possibilities might further improve prognosis. Population benefits from recurrence prevention are limited, because of the relatively high first stroke fatality and relatively low recurrence risk. The effects of increasing cardiac disease prevention and treatment are already evident and will further increase survival. The influence of demographic changes differs between the Netherlands and the USA. Stroke prevalence will increase less in the USA, due to a less extreme aging of the population. For blacks, stroke incidence and morbidity rates are higher. However, for this group mortality decline parallels the decline for whites\(^4\). With a mortality trend of the same magnitude, similar dynamics in stroke morbidity might be taking place. These issues can only be dealt with after including population-specific transition probabilities and demographic and epidemiological trends in the state-event model, which is possible.

In conclusion, this study supports evidence of a further decline in stroke incidence. It also supports the observation (Malmgren et al., 1989) that a further improvement of survival of higher age groups due to therapeutic interventions may result in a longer period of severe disability before death. The findings are of importance for setting health care priorities regarding the aged, especially regarding the nursing needs of stroke patients during the acute, rehabilitative and chronic phase of their illness.

**APPENDIX**

*Testing the goodness-of-fit* Age-specific computed stroke figures are compared with the national registry figures. This is done by using the standard formula for the chi-square test for larger tables: \(X^2 = \frac{(O - E)^2}{E}\), d.f. = (C-1) (Kirkwood, 1988). Here \(O\) represents the observed figure in both groups of data and \(E\) the expected figure. \(E\) is based on the calculation \((R \times N)/T\) where \(R\) is the sum of the computed and the registry figure for the age group involved, \(N\) is the total of all age groups, and \(T\) the total for all age groups of the computed and registry figures together. \(C\) is the number of age groups. The number of degrees of freedom is the product of the number of age groups minus 1 and the number of categories (i.e. computed and observed) minus 1.
REFERENCES

12. Dutch TIA Trial Study Group (1991): A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke, NEJM 325 1261-6.
6.1 SUMMARY

Introduction This chapter describes stroke occurrence in relation to its treatment. There is international consensus emerging on the contributions of trombolytic therapy, stroke units, and secondary prevention in improving stroke survival. The study presents the lifetime effects and medical costs of these interventions for the average stroke patient and identifies the optimum intervention mix.

Methods We apply the multi-state stroke model that distinguishes states after a first transient ischemic attack, a minor and a major stroke. It includes empirical utility weights for stroke disabilities and 5-year follow-up data on health care utilization and costs. It is used to compute lifetime costs and QALYs lived, by stroke state. We add pooled effectiveness and costs data for the three interventions. The table computes QALYs-lived and costs under the seven possible intervention mixes, including uncertainty distributions. A stochastic league table of the mixes presents the results in comparison to the non-intervention baseline.

Results Baseline results vary by age and sex - up to 2.7-3.7 times for QALYs lived and up to 1.4-2.0 times for cost. Stroke patients may gain a maximum of 0.5 QALYs per lifetime by the three combined interventions. Cost per QALY gained is lowest at younger ages for the stroke units and secondary prevention combined: for men about €55,000 and for women €73,000. Changes in costs and effects are small in comparison to the uncertainty ranges. All intervention mixes that include stroke units will most likely be the optimum choice.

Conclusion In spite of many uncertainties, it is shown that the development of acute stroke units deserves priority above medical therapies.
6.2. INTRODUCTION

Stroke is a major cause of disability and death in aging populations, leading to high health care costs (Murray and Lopez, 1997; Meerding et al, 1998; Holloway et al., 1999). In some countries in the late stage of the health transition, secular decline in stroke mortality appears to level off (Wolf et al., 1992; Wolf et al., 1992; Shahar et al., 1997; Barker et al., 1997; Reitsma et al., 1998). Given this possible compression of stroke mortality, it is a present challenge to reduce stroke disability (Fries, 1989; Niessen et al., 1993). Consequently, reduction of severe stroke disability may lead to a reduction of health care costs (Bonneux et al., 1998).

During the past decade, promising therapeutic options in stroke care have appeared. Consensus guidelines are already recommending widespread implementation (Adams et al., 1996; ECM, 1996; Pessin et al., 1997). Yet, there are debates. There is one on the effectiveness, feasibility and pre-requisites for thrombolysis to treat patients within three hours after the onset of stroke (NINDS, 1995; Hacke et al., 1998; Wardlaw and Warlow, 1999; Jorgensen et al., 1999). Others are on the health effects and requirements of stroke units (SUTC, 1997). Options in secondary prevention are increasing and might compete in effectiveness with acetylsalicylic acid (ATC, 1994; Matchar et al., 1994; Algra et al., 1998).

Demographic changes will lead to even higher numbers of stroke patients and the new medical technologies are leading to a higher demand for stroke resources. The premise of economic analyses is that, for any given level of resources available, one wishes to maximise the total aggregate health at the population level (Weinstein et al., 1977 & 1996; Granata and Hillman, 1998). In another more standardised approach, the World Health Organisation proposes to compare health effects and costs of optional intervention mixes against a baseline disease level. Generalised comparisons of interventions provide evidence on population benefits in relation to associated costs and may lead to more informed priority setting, also in allocating for stroke care (Murray et al., 2000; Hutubessy et al., 2001).

We describe the occurrence of stroke and related costs of care from a, population-based, health care perspective. Next, we analyse changes in stroke survival and medical costs under combinations of three interventions: thrombolytic therapy, acute stroke units, and secondary stroke prevention. We do this in a consistent way for the three interventions, with the remaining life span of the average stroke patient as time horizon.

6.3. MODEL DESCRIPTION AND SCENARIO DATA

Multi-state stroke model
We applied a multi-state life table model that has been used to describe the epidemiology of stroke in the Dutch population by age and sex (Niessen et al., 1993). Several papers have described this methodology (Niessen et al., 1993; Bonneux et al., 1998; Barendregt et al., 1997). The life table describes the disease history of stroke. It computes survival and death of patients by three linked stroke disability states: no disability, minor disability (Rankin scale score < 3) and major disability (Rankin scale score ≥ 3) (Niessen et al., 1993). It does so according by age and sex. They may enter one of the three states after a
transient ischemic attack (TIA), leading to no disability, or a stroke, leading to a minor or major disability. Death risks in all states include death from stroke, cardiovascular disease, and all other diseases. It calculates all surviving patients in each stroke disability state, in time steps of half a year, until all patients have died. Patients may change health states after the first event. The table comprises risk of disability after one month, recovery from major disability at six months and risks of recurrent events and severe disability during the first year and during all other years.

For our analyses, we multiply the patient numbers for each disability state by quality-of-life weights for minor and major stroke. Added up, this yields the total of quality-adjusted life years (QALYs) lived by all three types of stroke patients. We also multiply these patient numbers with the medical cost estimates for each state for each half a year after stroke. The cost estimates are the product of health care utilization data per patient per state for each per year, and full costs per unit per health care service. This leads to an estimate of the average lifetime costs per patient.

We re-calculated the health effects and costs attributable to the stroke interventions by adapting the stroke table risks for mortality, disability, recovery, and recurrence accordingly and adding the intervention costs. The life table recalculates the survival of patients and the number of years lived in each state and the total stroke costs. The difference with the baseline computation generates the changes in quality-adjusted years and in costs for each stroke state and for the average stroke patient.

To validate the life table for the baseline situation we have compared model-generated age and sex-specific figures on stroke events and mortality to the national empirical figures on acute hospital admissions and stroke mortality for the year 1985 (Niessen et al., 1993). We also validated computed major stroke prevalence against data from the national nursing home registry of the same period.

**Input data on effectiveness of interventions**

In consensus meetings, we have selected effectiveness data from published meta-analyses (Table 6.1). (Limburg, 2000) We have added values from studies that allowed us to make an estimate of the effectiveness of the intervention in common practice i.e. beyond a randomized trial setting. We used the reported confidence intervals to estimate the probability distributions of the intervention effect, assuming a normal distribution (Briggs and Fenn, 1998; Briggs and Gray, 1998). For thrombolysis, until now, only recombinant tissue plasminogen activator (r-TPA) is shown to be effective (Wardlaw and Warlow, 1999). Given within three hours after stroke it improves the outcome of acute stroke after three months (Wardlaw and Warlow, 1999; Hacke et al, 1998; NINDS, 1995). This is also the case in non-experimental settings (Chiu et al., 1998). In a meta-analysis, we pooled the data of the three randomized studies. In the control group of 284 patients 52 died, among the 294 patients in the r-TPA group 50 patients died. In the r-TPA group 184 patients had a Rankin score < 4; in the control group only 154 patients had this score (Niessen et al., 2000). The small number of patients treated leads to an odds ratio for reducing the number of patients with a Rankin score ≥ 3 with a large confidence interval. We assumed that 10% of patients are eligible for thrombolysis, although the literature reports figures between 5-8%. 

\[ \text{odds ratio} = \text{number of patients in control group with rankin score } \geq 3 / \text{number of patients in r-TPA group with rankin score } < 4 \]
Stroke care

<table>
<thead>
<tr>
<th>Intervention option and survival variable</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trombolysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual major disability at three months</td>
<td>0.68 (0.46-1.00)</td>
<td>Hacke, 1998; Wardlaw, 1999</td>
</tr>
<tr>
<td><strong>Stroke unit care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute case-fatality</td>
<td>0.87 (0.79-0.96)</td>
<td>Stegmayer et al., 1999</td>
</tr>
<tr>
<td>Residual disability at 24 weeks</td>
<td>0.79 (0.56-1.10)</td>
<td>Kwakkel et al., 1999</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of recurrent stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA† versus placebo</td>
<td>0.77 (0.61-0.96)</td>
<td>ATC, 1994</td>
</tr>
<tr>
<td>ASA + dipyridamol versus placebo</td>
<td>0.62 (0.45-0.70)</td>
<td>Matchar et al., 1994</td>
</tr>
<tr>
<td>ASA + dipyridamol versus ASA</td>
<td>0.84 (0.64-0.96)</td>
<td>Algra, 1998</td>
</tr>
<tr>
<td>Risk of cardiovascular death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA versus placebo</td>
<td>0.88 (0.64-1.21)</td>
<td>ATC, 1994</td>
</tr>
<tr>
<td>ASA + dipyridamol versus placebo</td>
<td>0.79 (0.49-1.21)</td>
<td>Matchar et al., 1994</td>
</tr>
<tr>
<td>ASA + dipyridamol versus ASA</td>
<td>0.99 (0.86-1.65)</td>
<td>Algra, 1998</td>
</tr>
</tbody>
</table>

Table 6.1. Pooled odds ratios from meta-analyses by stroke intervention and stroke survival variable. † ASA: Acetylsalicylic acid.

Stroke units lead to an improvement in stroke survival and stroke disability (SUTC, 1997; Indredavik et al., 1999; Stegmayer et al., 1999). Two long-term follow-up studies show persistent improvements of stroke survival and disability level (Indredavik et al., 1999; Jorgensen et al., 1999). Our stroke unit care scenario includes reductions in acute fatality and in risk of a permanent severe disability, assuming a lifelong effect. In addition, we included more intensive nursing and rehabilitation in the acute phase, a length of hospital stay of 14 days and intensive rehabilitation until six months after onset (Kwakkel et al., 1999).

Medical secondary prevention after stroke leads to reductions of both recurrent stroke and of cardiovascular mortality after a first TIA or first stroke (ATC, 1994; Matchar et al., 1994; Dippel, 1998; EAFT, 1993). We did not include disability or costs resulting from cardiovascular events. The effects of secondary prevention decrease during the years after the first stroke, possibly due to mortality selection or lack of patient compliance (ATC, 1994; Matchar et al., 1994; Dippel, 1998; EAFT, 1993). In our model, we incorporated the costs and effects of prevention during the five years after the initial stroke.

Input data on cost estimates Table 6.2 gives an overview of data used, published in our cost study (Bergman et al., 1995). The data include all medical costs after a first stroke related to hospital treatment, institutionalisation, rehabilitation, primary care, and home care. As the model distinguished two stroke states, we differentiated the cost data by these categories. For hospital settings, this is already known but not for the follow-up period. The same study, however, collected data on the distribution of surviving patients after a first stroke among nursing homes, rehabilitation centres, and their own homes, during a five-year follow-up. We re-analysed the data set to find a rate of institutionalisation, by initial stroke severity and by period after a first stroke (van Straaten et al., 1997; Scholte op Reimer et al., 1999). Almost no patients with a minor stroke stayed in an institution. After six months 29.1% (95% CI: 25.1-33.2) of the men with a major stroke stayed in an institution and 38.8% of the women (95% CI: 34.9-42.9). After that period
institutionalisation stabilized among both men (16.5%; 95% CI: 12.6-20.4) and women (26.9%; 95% CI: 22.3-31.5).

Some additional estimates of the additional costs of stroke units and intensive physiotherapy needed to be collected in a separate costing study on the Rotterdam Stroke Services. (Niessen et al., 2000) Other outpatient cost estimates for medical treatment are based on official reimbursement rates (Table 6.2).

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Academic hospital</th>
<th>General hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Euro per day</td>
<td></td>
</tr>
<tr>
<td><strong>Institutional costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission after minor stroke</td>
<td>264</td>
<td>196</td>
</tr>
<tr>
<td>after major stroke</td>
<td>310</td>
<td>224</td>
</tr>
<tr>
<td>after fatal stroke</td>
<td>426</td>
<td>252</td>
</tr>
<tr>
<td>Home care first six months</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>after six months</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Nursing home admission</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td><strong>Additional costs of hospital interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-TPA treatment *</td>
<td>2,385 (1,789-2,981)</td>
<td></td>
</tr>
<tr>
<td>Stroke Unit * †</td>
<td>61 (44-78)</td>
<td>42 (32-53)</td>
</tr>
<tr>
<td>Intensive rehabilitation †</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Euro per month</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Additional costs of extramural interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive physiotherapy or occupational therapy †</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>ASA powder, 38 mg; tablets 100 mg ‡</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Dipyridamol Retard caps, 400 mg ‡</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Dipyridamol + Acetylsalicylic acid, 325 mg ‡</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Pharmacy prescription charge §</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>General physician prescription charge #</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.2. Institutionalisation and costs of stroke care according to type of Intervention, hospital type and period after stroke onset.

* Costs of procedures and medication (uncertainty range ± 25%) (Niessen et al, 2000); Sources: † Rotterdam Stroke Service study; ‡ Insurance Council; § Royal Dutch Society of Pharmacists; #Dutch Society of Family Physicians. ASA= Acetylsalicylic acid

Input data on utility weighing for stroke disability We have applied utility weight distributions for minor and major stroke disability as defined by the Rankin scale (Niessen et al., 1993; Gold et al., 1998). For this, we used the EuroQol scale, shown valid in stroke patients (Dorman et al., 1997). We have assessed the disability status of 129 stroke patients (mean age 69 years) in two Rotterdam hospitals using both the Rankin scale and the five-dimensional EuroQol scale. The follow-up lasted up to six months after hospital admission. The total number of measurement pairs was 248. The measurements correlated well and are consistent during the time after stroke. Using the individual EuroQol scores, we calculated the average utility value and the average Rankin score for both minor and major stroke disabilities. The point utility value for minor stroke disability is 0.72 (SD=0.23) and for major stroke 0.47 (SD=0.31). For our analyses, accounting for uncertainty, we used the distribution of utility values from the original
EuroQol data set given the two observed point utility weight score (Dorman et al., 1997; Dolan, 1997).

**Stochastic league table methodology**

Our analysis compares the relative efficiency of each intervention sets. Given a budget level, it selects the most cost-effective option first. If there is budget left for more options, it chooses the next cost-effective options, etc, until the budget is exhausted. To allow for this, we first computed lifetime health effects and costs for the baseline and seven intervention sets for stroke at 60, 70 and 80 years of age, by sex. Combinations of the three interventions define the sets. Each of the sets includes all possible (seven), mutual exclusive, mixes of intervention options, and the baseline scenario (Table 6.3). To account for uncertainties in estimated effects and cost, we included all uncertainty ranges in the input values for effectiveness, costs, and utilities. (Tables 6.1-3 and Input data sections) The normal distributions have been truncated and entered in a random sampling procedure, using @Risk-Excel-software.

Next, the outcome distributions for QALYs and costs, generated in the multi-state life table, have been used in the stochastic league table approach. Their point estimates and standard deviations define these distributions (Table 6.3). The league table technique applies also random sampling (up to 10,000 iterations) to draw from generated distributions. Here, we made the, common, assumption that costs have a lognormal distribution and health benefits have a normal distribution. We use a software program called MCLeague, described elsewhere (Hutubessy et al., 2001). Using the results of each draw from the outcome distributions, it computes the cost-effectiveness of the intervention mix options in each set, compared to baseline. Next, it decides which combinations of mixes are to be included in the optimum package, given a budget ceiling. We treat the six sets of interventions as independent. This supposes that one can implement one without influencing the outcomes and /or costs for the other group of patients (Murray et al. 2000). This means that, if additional packages are possible, given the budget available, these are included too. The league table presents the results of our comparative CEA. It indicates the probability that a specific intervention would be included in the optimal mix of interventions given a particular level of resource availability.

### 6.4. RESULTS

Table 6.4 shows the calculated lifetime costs and QALYs lived by intervention mix as point estimates. As the standard deviations vary little between intervention mixes, we only have listed the average standard deviations in the Table 6.3. This is to simplify the presentation. In our uncertainty computations, we use the individual estimates. Outcomes by age and sex vary up to 2.7-3.7 times the number of QALYs lived and up to 1.4-2.0 times the lowest lifetime costs. At age 60, the average stroke patient gains a maximum of 0.5 QALYs per lifetime from all combined interventions (Figure 6.1). Differences in health gain between the sexes are due to differences in absolute cardiovascular risks and remaining life expectancies. The table shows that all mixes lead
either to cost savings or to low additional costs as compared to baseline and, hence, lead to more efficient stroke.

Trombolysis is indicated in only a small group of patients. It adds the lowest number of QALYs: about 0.1 per average stroke lifetime. Secondary prevention is about twice as effective, preventing both strokes after transient attacks and recurrent minor strokes, still a minority of the stroke population. Stroke units, as a single intervention package, or in combinations, yield about four times as many QALYs per lifetime.

Cost differences between major and minor stroke patients (not shown) vary between 2.5 and 2.9 for men and for women between 3.8 and 4.2 (Niessen et al., 2000). These differences are largest at younger ages as patients survive for a longer period. Our results compare with previously estimated Dutch average for all strokes (Bergman et al., 1995).

Institutionalization dominates lifetime costs. (Bergman et al., 1995; van Straaten et al., 1997). For comparison, in the United States the average lifetime costs of stroke are €49.000 for ischemic strokes at 65 years of age and €26.000 at 85 years, for men. For women this is €52.000 and €26.000 (Taylor et al., 1996).

Changes in costs and effects are small in comparison to the computed uncertainty ranges (Table 6.3). The next section deals with selecting the optimum stroke package, given these uncertainties.

6.5. STOCHASTIC LEAGUE TABLE FOR STROKE CARE

Figure 6.1 shows the same point estimates in a so-called cost-effectiveness plane, by intervention mix. For each mix, both average health gain and average costs are higher in younger age groups and are higher among the women. Figure 6.1 clearly shows that stroke units give more benefit at slightly higher costs. It is most effective at younger ages. Here, cost per QALY gained is lowest for the mix including stroke units and secondary prevention: for men about €55.000 and for women €73.000. The plane demonstrates that trombolysis leads to relatively little average benefit at high average cost (the cost of institutionalisation of those not indicated for treatment). The same holds for secondary prevention as a single intervention. Here, cost-effectiveness ratios are over €100.000 per QALY gained. Their combination leads to as much health gain as stroke unit care at older ages.

Trombolysis and stroke units give immediate health benefits to the patient. When the age of stroke onset rises, there are fewer years without disability to gain and, consequently, cost-effectiveness of these treatments decreases with age. Optimum packages at lower budget levels would exclude these interventions at older ages.
Table 6.3. Lifetime mean quality-adjusted life years lived and medical costs after a first stroke by stroke intervention mix. Bottom line shows standard deviations. ‘SP’ = Secondary Prevention; ‘rTPA’ = thrombolysis; ‘SU’ = Stroke unit care; ‘SD’ = standard deviation. Costs are in 1996 Euros. Discount rate for costs 3%.
Secondary prevention has delayed effects and yields more health benefits at higher ages, as the risks of recurrent stroke are higher. Hence, also due to its low costs, its cost-effectiveness increases with age and leads to cost savings. Here, optimum packages at low budget would exclude younger ages.

Lifetime costs (Euros)

![Graph showing lifetime health gain and total medical costs as compared to baseline by intervention mix (by age and sex; same markers; see Table 6.3. for values). 'SP'= Secondary Prevention; 'rTPA' = thrombolysis; ‘SU’= Stroke unit care; ‘SD’= standard deviation. Discount rate costs 3%.

Figure 6.2 gives the probability of each intervention mix to be included in the optimum stroke package by age and sex, using the stochastic life table approach. At the higher budget range (€150,000), interventions at all age and sex groups are relevant. Here, also the less cost-effective options can be included and the probabilities for each option, in each set, stabilise. At the high budget level, one can observe that any intervention mix that includes stroke units is most likely the optimum choice. Adding thrombolysis or secondary prevention, actually, would not make a big difference, given uncertainties. At lower budget levels, younger age groups are, indeed, included in the optimum stroke package. One can also observe an interaction effect between thrombolysis and stroke unit care: the combined effect is less that the added effect of the two options. If patients improve more because of one intervention, on average, there is less to gain from the second.
Figure 6.2. Probability to be the optimal mix for the various stroke intervention options by available budget level. Stochastic league table analysis (MCLeague, Hurubessy et al., 2001). ‘SP’= Secondary Prevention; ‘rTPA’ = thrombolysis; ‘SU’= Stroke unit care.
6.6. DISCUSSION

We conclude that stroke units and medical therapies after stroke are cost saving or are cost-effective as compared to a non-intervention situation. The medical therapies are effective for small patients groups only. Costs per QALY gained are higher in stroke units than for medical therapies, yet stroke units yield higher population benefits. The organization of specialized stroke unit care deserves more priority that until now is given. Our conclusion stands, even considering all relevant uncertainties.

The introduction of a stroke unit is a complex intervention. Most effectiveness research from Europe shows an improvement in stroke survival and handicap, and institutionalisation rate (SUTC, 1997; Indredavik et al., 1998; Jorgensen et al., 1999). This improvement does not depend on age (Falconer et al., 1994; Kalra, 1994). The few existing long-term follow-up studies after stroke unit care show a persistent improvement of stroke survival and disability (Indredavik et al., 1999; Jorgensen et al., 1999). In the United States, little evaluation research is available (Pessin et al., 1997; Lincoln et al., 1996; Lee et al., 1996). This has been less systematic (Asplund, 1997) and clinical trials show a large design effect (Ottenbacher and Janell, 1993). Stroke unit care deserves to be a priority also in this country (Gresham et al., 1997).

One other relevant intervention, primary prevention of the major risk factor, hypertension, might yield more effective and even more cost-effective results, especially when co-existing risk factors like diabetes are treated as well. We did not include treatment of hypertension in our analysis, as there is a lack of consistent data.

Costs of stroke

In comparison to previous studies (Bergman et al., 1995; Taylor et al., 1996), we have shown that lifetime costs of stroke by age of onset and sex differ according to initial severity. In cost-effectiveness calculations of stroke interventions, one has to account for these differences.

The results of our study and a previous one for the Dutch situation are consistent. Our league table estimates are rather robust to changes in probability of nursing home admissions. For comparison, in the United States the average lifetime costs of stroke are $49,000 for ischemic strokes at 65 years of age and $26,000 at 85 years, for men. For women this is $52,000 and $26,000 (Taylor et al., 1996). The average direct costs for a Medicare stroke patient lies in the similar range of magnitude as ours. We contribute this consistency to similar distributions of patients by sex and by residence. In Rochester among 218 patients admitted to nursing homes for the first time, 24% had been admitted for 91-365 days and 21% for 1-5 years after the stroke, as measured in residence days (Brown et al., 1999). In the UK, after a 4.9 years follow-up, the distribution of patients is comparable with 29% of the survivors severely or moderately disabled, 37% were mildly disabled, and 34% were functionally independent (Wilkinson et al., 1997).

For the same reason, including productivity costs to communities would not influence the relative cost-effectiveness values. On the other hand, early discharge from stroke units with professional support might increase the burden for kith and kin (Scholte op Reimer, 1999). We did not use a human capital approach, (Taylor et al., 1996), which leads to, in our opinion, unrealistically high indirect cost estimates.
**Stroke care**

Cost-effectiveness methodology

Cost-effectiveness analyses of single stroke interventions are common and increasing. Outcomes are difficult to compare because of lack of standardisation and different referent populations. The population perspective and the use of a baseline make our approach consistent and allows for comparisons of different stroke interventions in different subgroups.

We compare the interventions against a baseline situation and choose the year 1985 as our reference situation. The assumption is that the studied interventions have become, or will become fully, effective in the Netherlands after this year. This is probably true for the medical therapies. Specialised stroke care probably started, gradually and earlier on an unknown scale. In our calculations, however, we consider the additional effort to be made (Limburg, 2000). For other countries, health gains as well as the additional costs of stroke units will most likely be bigger.

We used public utility values for minor and major disabilities. In another study, many patients at risk for stroke considered major stroke worse than death, i.e. a utility value lower than 0 (Samsa et al., 1999). The average utility value for major stroke in this study was 0.23 with a large spread of values. The utilities depended on how one rates one’s presence status and how one rates living with severe disability. At older ages, utility values influence cost-effectiveness results more than at younger ages. As stroke units become less cost-effective with at older ages, it becomes important to consider patients’ preferences (Gold et al., 1998). In our analysis, lower utility values for major stroke would influence all our results in the same way and would not alter our conclusions.

**Conclusion**

We have compared the (combined) effects of three types of treatment after stroke on lifetime stroke disability and lifetime costs of stroke. The selected treatments reduce disability, and may be cost-saving or cost-effective for the analysed patient groups. Uncertainties in our outcomes exist on intervention effectiveness and costs, institutionalisation rate, indirect costs and disability weighing. They affect the analyses in the same way and do not affect the population benefit ranking of the interventions. Our main conclusion - intensive care for stroke patients deserves priority - remains valid in spite of the large number of inherent uncertainties that we have shown.
REFERENCES


42. Niessen LW, Dippel DW, Limburg M (2000): [Costs estimates after stroke and cost-effectiveness of stroke units and secondary prevention, as recommended in the revised CBO stroke guidelines], Ned Tijdschr Geneeskd 144 1959-64.
CHAPTER 7

LATE TRANSITIONAL MORBIDITY: DIABETES COMPLICATIONS

7.1. SUMMARY

Introduction This chapter reports multi-state modelling in a guidelines development setting. In the Netherlands a program on quality assurance in medical care has started in 1996. Clinical professionals, patient organizations and health services researchers formulate evidence-based guidelines with a concomitant cost-effectiveness analysis. This application examines the cost-effectiveness of guideline recommendations for prevention of nephropathy in diabetes mellitus type 1 and 2.

Methods A Markov multi-state model was developed. Data from international publications on epidemiological surveys and randomized trials, together with national data on health care use and costs, were used to feed the model. A cohort of diabetes patients without renal disease enters the model. Outcome measures are complication (end-stage renal disease) free years, QALYs, and lifetime medical costs per patient treated according to guideline recommendations or current anti-diabetic strategy.

Results Guideline treatment for type 1 diabetes yields 4.2 complication-free life years, at a cost-effectiveness ratio of 13,500 Dutch guilders per QALY gained. Type 2 diabetes patients gain 0.2 complication free life years at a cost-effectiveness ratio of 31,000 Dutch guilders per QALY gained.

Conclusion Guideline development for diabetes nephropathy, with concomitant cost-effectiveness calculations, has resulted in a transparent guideline with explicit information on long-term cost and effects. The project has brought health care providers and health services researchers together in health modelling.
Chapter 7

7.2. INTRODUCTION

The principles of managed care and shared financial risks in health care, urge for the integration of medical care and health economics in policy making (Power and Eisenberg, 1998). Over the past decades guideline development has changed from opinion based to evidence-based guidelines, with increasing attention for health-economics in the guideline development process (Mason et al., 1999). Ideally, a cost-effectiveness data should be incorporated in the process of developing recommendations on treatment measures. In practice there is no clear manner to incorporate cost-effectiveness data in the guideline development process. A national project “Quality Assurance In Medical Care” was launched in the Netherlands in January 1998. The program is a joint effort from (para) medical professional organisations, patient organisations, health economists and other health services researchers, to formulate evidence based guidelines with a concomitant cost-effectiveness analysis (CEA) and a strategy for implementation in daily medical practice (Casparie, 1999). The project has been initiated by the Dutch Ministry of Health and implemented by the National Organisation for Quality Assurance in Hospitals, the WHO Collaborating Centre for Quality Assurance in Health Care and the Institute for Medical Technology Assessment. Although the project has a national character, international collaboration and sharing of information has been exploited. Not a single country can conduct all MTA (multi-state modelling) studies on its own (Borst-Eilers, 1997).

Quality assurance in integrated diabetes care is one of the first subjects to have been dealt with in the project. After literature searches on effectiveness of interventions, (para)medical professionals and patient organisations formulate guidelines on prevention of diabetes nephropathy, through informal consensus meetings (Ballard et al., 1988). Draft versions of the guideline were submitted to cost effectiveness analyses at an early stage. This setting has supported the interaction of health scientists and medical professionals in promoting cost consciousness in diabetes care (Ballard et al., 1988).

Diabetic nephropathy is a micro-vascular complication of both insulin dependent (type 1) and non–insulin dependent (type 2) diabetes mellitus. In diabetes patients, development of nephropathy is a gradual process with distinct stages of micro– and macro–albuminuria, before end stage renal disease (ESRD) might develop. Without intervention the cumulative incidence of diabetic nephropathy after twenty-five years is 25 to 35 percent (Ballard et al., 1988; Nelson et al., 1995). Randomized trials have shown that diabetic nephropathy in both type 1 and type 2 diabetes patients can be prevented, or progression slowed down by optimal glycemic control, blood-pressure control and the use of ACE–inhibitors (DCCT, 1993; Lewis et al., 1993; UKPDS, 1998). The annual incidence of end stage renal disease due to diabetic nephropathy, needing dialysis, in the Netherlands is 11.2 per million inhabitants.[10] This contrasts with an incidence of 58.9 per million inhabitants in the United States. In the latter country, 30% of the dialysis patients are due to diabetic nephropathy. In 1996 in the Netherlands, 15.5% of the 1,332 new dialysis patients were due to diabetic nephropathy (Nelson et al, 1995; Renine, 1998).
In the national quality assurance project, guidelines for primary and secondary prevention of nephropathy, retinopathy and neuropathy in diabetes mellitus type 1 and type 2 have been formulated. Focus–points of the new guidelines are: intensive insulin treatment and complication specific care. Annual screening of urine for micro–albuminuria, ACE inhibitors in advanced micro–albuminuria, treatment of hypertension and reinforcement of a healthy lifestyle, are recommended to prevent diabetes nephropathy (CBO/NDF, 1998). In this paper the long–term costs and effects of current treatment strategies are compared with the long–term costs and effects of treatment following guidelines.

7.3. MODEL DESCRIPTION AND VALIDATION

The long duration between the onset of diabetes and the development of nephropathy and the lack of national epidemiological data urges the use of modeling techniques to study possible effects and costs of interventions in the Dutch situation (Buxton et al., 1997). A Markov multi-state model was developed using Quattro Pro for Windows (the model can be made available on request). A flowchart of the model, describing four health states and seven possible transitions (1–7), is given in Figure 7.1. A separate analysis is performed for type 1 (insulin dependent diabetes diagnosed before the age of 30 years) and type 2 diabetes (all diabetes diagnosed after the age of 30 years) (Lewis, et al., 19993; Ruwaard, 1996; DCCT, 1996).

![Figure 7.1. Disease states of the diabetes nephropathy model for both types of diabetes.](image)

A prevalence cohort consisting of 100 hypothetical diabetes patients, without renal complications enters the model. Epidemiological and clinical characteristics of the cohort match characteristics of prevalent type 1 and type 2 diabetes patients in the Netherlands without renal complications. The average age of incidence for diabetes (clinical diagnosis) in the Netherlands is 15 years for type 1 diabetes and 55 years for type 2 diabetes. The average age of the prevalence cohort entering the model is 21 years for the type 1 diabetes and 62 years type 2 diabetes (DCCT, 1993; Klein, 1995; Ruwaard and Kramers, 1996).
The model simulates the course of the disease in steps of one year. At the end of each year, cohort members can progress to the next health state or die, or they remain in the same health state. Albuminuria health states are defined laboratory test outcome conditions. End stage renal disease is a health state defined by the need of renal replacement therapy; continuous peritoneal dialysis (CAPD), hemo-dialysis or renal transplant.

<table>
<thead>
<tr>
<th>Cost item</th>
<th>diabetes type 1</th>
<th>diabetes type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>annual costs (Dfl)</td>
<td>Sources</td>
</tr>
<tr>
<td><strong>Current care</strong></td>
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<td></td>
</tr>
<tr>
<td>GP visits; 32 NLG / unit</td>
<td>64</td>
<td>Bilo, 1996</td>
</tr>
<tr>
<td>Specialist visits (fixed annual fee)</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td>Laboratory</td>
<td>192 (a)</td>
<td>40 (b)</td>
</tr>
<tr>
<td>OPD running cost nurses; 14 NLG / unit</td>
<td>64</td>
<td>14</td>
</tr>
<tr>
<td>overhead cost (fixed annual cost)</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Insulin, materials &amp; self control</td>
<td>1860</td>
<td>72 (c)</td>
</tr>
<tr>
<td><strong>Extra care following guidelines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP visits; 32 NLG / unit</td>
<td>--</td>
<td>64</td>
</tr>
<tr>
<td>Telephone consultation</td>
<td>--</td>
<td>35 (d)</td>
</tr>
<tr>
<td>Laboratory</td>
<td>50 (e)</td>
<td>CBO/NDF</td>
</tr>
<tr>
<td>OPD running cost first year nurses; 14 NLG / unit</td>
<td>168</td>
<td>†</td>
</tr>
<tr>
<td>OPD running cost later years nurses; 14 NLG / unit</td>
<td>28</td>
<td>†</td>
</tr>
<tr>
<td>Insulin, materials &amp; self control</td>
<td>1,100</td>
<td>CBO/NDF</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>395</td>
<td>Lewis, 1993</td>
</tr>
<tr>
<td><strong>Renal replacement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dialysis (f)</td>
<td>133,400</td>
<td>Wit, 1997</td>
</tr>
<tr>
<td>Tx first year</td>
<td>90,400</td>
<td>Bilo, 1996</td>
</tr>
<tr>
<td>Tx later years</td>
<td>36,600</td>
<td>Wit, 1997</td>
</tr>
</tbody>
</table>

Table 7.1. Estimated annual health care costs per patient by cost item for diabetes type 1 and type 2. GP = general practitioner; Tx = renal transplantation. CBO/NDF guidelines development commission
(a) 4x HbA1c, blood glucose, electrolytes, creatinin, urea, 1x lipid spectrum.
(b) 4x blood glucose control, 1x micro–albuminuria screening (Cromme et al., 1996).
(c) weighted average of diet only, oral hyperglycaemic treatment and insulin/self control.
(d) 2 calls / week with a diabetes nurse, 3 min / call.
(e) 8x blood glucose, 1x screening micro–albuminuria.
(f) weighted average of three types of hemodialysis (active, passive and peritoneal dialysis).
† written communication from the diabetes nephropathy guideline development committee.

Disease progression and mortality are quantified by annual transition probabilities representing an average chance on progression or mortality. The transition probabilities (Appendix) are derived from international studies and national statistics (Lewis et al., 1993; Renine, 1998; DCCT, 1996; Bilo, 1996; Eastman et al., 1997a; Eastman et al., 1997b, Rossing et al., 1996; Schmitz and Vaeth, 1988). Transitions 1 and 2 are adjusted to the
Diabetes morbidity

Dutch situation, by multiplying them with a HbA1c related converting factor, as used by Eastman et al. (1997). In the United States the average HbA1c value for patients on regular treatment is 9.0% for type 1 and 10.0% for type 2 diabetes (Eastman et al., 1997; DCCT, 1995). Studies in the Netherlands report an average HbA1c of 8.27% among type 1 diabetes patients and 7.6% among type 2 diabetes patients (Sonnaville et al. 1997; Bilo et al., 1996; Assink, 1997). In daily practice, effectiveness of treatment measures recommended in guidelines, will improve the HbA1c levels to 7.2% and 7.0% respectively (Eastman et al. 1997; DCCT, 1995). Disease progression in patients receiving current treatment differs from disease progression in patients receiving intensive blood glucose treatment and ACE-inhibitors. In the model this difference in disease progression results in different transition probabilities between health states, for current and guideline treatment modalities.

In comparing the current level of care with intensive blood glucose treatment and ACE-inhibitors, we use a health care perspective. This means only direct medical cost and direct health effects –defined as complication (ESRD) fee life years gained– are considered. The costs and effects of the guideline treatment are modeled through costs and effects of intensive treatment and ACE–inhibitors in macro–albuminuria. To reflect the intensity of blood glucose control, the average HbA1c level is used. Data on the present use of ACE–inhibitors by diabetes patients in the Netherlands are not available; we have assumed that no ACE–inhibitors are being used in the current treatment scenario. A summary of cost data used in the study is given in Table 7.2. For type 1 diabetes the cost incurred by standard treatment, are based on actual expenditure data derived from a Dutch survey (Bilo, 1996). Unit prices under guideline care are the same as unit prices in current care. For guideline treatment, follow–up frequency during the first year is 16 specialist visits. In later years four to six follow–up visits will be necessary to monitor intensive insulin treatment and the effect of ACE–inhibitors. Data on service use by type 2 diabetes patients are derived from studies comparing standard treatment with intensive treatment protocols, in general practices in the Netherlands (Sonnaville et al., 1997; Bilo et al., 1998). To calculate the costs for ESRD patients a weighted average of actual costs incurred for hemo-dialysis, peritoneal dialysis and renal transplant patients was used (Renine, 1998; Wit and Charro, 1997).

7.4. RESULTS

Results with and without discounting are presented in Table 7.2. After ten years of guideline treatment a health effect becomes evident. The health effects of the guidelines accumulate to a maximum over a lifetime (see Appendix), which is set at 50 years for type 1 diabetes cohort and at 30 years for type 2 diabetes cohorts. At this time virtually all members of the type 1 and type 2 diabetes cohorts will have died. In the type 1 diabetes cohort of 100 patients without renal complications, introduction of intensive insulin treatment results in 2.9 complication free life years and ACE inhibitors in 0.4 complication free life years extra per patient in a lifetime. The cost–effectiveness ratio improves as the cohort ages and the effect increases (Figure 7.2). Introduction of intensive blood glucose control alone has a favorable cost–effectiveness ratio and introducing ACE
inhibitors in macro–albuminuria is cost saving. The cost–effectiveness ratio of 13 500 DFL per QALY gained, for introducing both treatment options combined, is favorable compared to other health interventions.

<table>
<thead>
<tr>
<th></th>
<th>intensive blood glucose control</th>
<th>ACE-inhibitors</th>
<th>both treatment measures</th>
</tr>
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<tbody>
<tr>
<td><strong>100 type 1 diabetes patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complication free years gained</td>
<td>2.9 (1.1)</td>
<td>0.4 (0.1)</td>
<td>4.2 (1.4)</td>
</tr>
<tr>
<td>QALYs gained</td>
<td>1.1 (0.7)</td>
<td>0.2 (0.04)</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td>Extra cost / patient / year</td>
<td>555 (365)</td>
<td>-350 (-175)</td>
<td>430 (310)</td>
</tr>
<tr>
<td>Cost / complication free year</td>
<td>9,500 (17,000)</td>
<td>Cost saving</td>
<td>5,000 (11,000)</td>
</tr>
<tr>
<td>Cost / QALY (3%)</td>
<td>25,000 (26,000)</td>
<td></td>
<td>13,500 (26,000)</td>
</tr>
<tr>
<td><strong>100 type 2 diabetes patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complication free years gained</td>
<td>0.2 (0.1)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>QALYs gained</td>
<td>0.08 (0.04)</td>
<td>0.0 (0.0)</td>
<td>0.08 (0.04)</td>
</tr>
<tr>
<td>Extra cost / patient / year</td>
<td>-10 (-5)</td>
<td>82 (66)</td>
<td>11,500 (16,500)</td>
</tr>
<tr>
<td>Cost / complication free year</td>
<td>12,500 (17,500)</td>
<td>Cost saving</td>
<td>31,000 (50,000)</td>
</tr>
<tr>
<td>Cost / QALY</td>
<td>33,000 (52,000)</td>
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Table 7.2. Overview of effects and costs for a cohort of 100 diabetes patients. Costs are in Dutch guilders (Dfl1996; 3% discounted); ESRD: end stage renal disease.

a Complication free life years are years without ESRD. Complication free life years are gained by guideline treatment over current treatment. (after 3% discounting).

b Utility for ESRD: 0.61. Utility for diabetes patients following current treatment strategies or intensive treatment is set at 1.00 and assumed the same for all treatment strategies (DCCT, 1996).

c The cost–effectiveness ratio.

Figure 7.2. Cost per ESRD-free life year gained (Dfl1996) by years of diabetes guidelines treatment in a hypothetical diabetes cohort without renal complications.
Diabetes morbidity

For the type 2 diabetes cohort of 100 patients without renal complications, the average lifetime effect of intensive blood glucose control treatment is 0.2 complication free life years per patient. Introducing ACE–inhibitors will not add a significant number of QALYs. Despite the small effect, introducing guideline measures yields a favorable cost–effectiveness ratio, because the costs involved are low as well. Again we see that the cost–effectiveness ratio of introducing the full guideline improves with time.

Estimates of the current HbA1c level among type 2 patients in the Netherlands vary between 7.6% and 8.6% (Sonnaville et al., 1997). The cost–effectiveness analysis for type 2 cohorts was performed twice, using both HbA1c estimates. It appears that the potential health gain depends largely on the HbA1c reduction achieved by guideline treatment. Varying the current HbA1c level in type 1 cohorts, shows the same trend. Another factor limiting the potential health gain in type 2 diabetes cohorts, is a high mortality in the various health states. This high mortality is due to high age and high cardiovascular mortality. The mortality does not improve by guideline treatment (UKPDS, 1998).

Validation

Validation of the model results was done using diabetes and dialysis prevalence data from national statistics. External validation results are presented in Table 7.3. For type 1 diabetes the number of prevalent dialysis patients calculated by the model (295 cases), using empirical data on diabetes prevalence from the Netherlands in 1994 (35 000), is comparable with the number of prevalent patients reported in the national dialysis register (231 cases). The number of prevalent dialysis patients, calculated using empirical data on diabetes incidence, is higher (460 cases). For type 2 diabetes the number of prevalent dialysis patients under the current treatment scenario calculated by the model, is higher than the number of prevalent dialysis patients reported by the national register (136 cases) (Renine, 1998; VTV, 1997; Baan et al., 1998).

<table>
<thead>
<tr>
<th>validation variable</th>
<th>empirical validation value (1994)</th>
<th>values generated by models based on current treatment level</th>
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<td>diabetes incidence</td>
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<tr>
<td>Type 1 diabetes</td>
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<td></td>
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<td>Diabetes prevalence</td>
<td>35,000</td>
<td>–</td>
</tr>
<tr>
<td>Diabetes incidence</td>
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<td>54,000</td>
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<tr>
<td>Dialysis prevalence</td>
<td>231</td>
<td>27,000</td>
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<tr>
<td>Type 2 diabetes</td>
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<td></td>
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<tr>
<td>Diabetes prevalence</td>
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<td>–</td>
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<td>Diabetes incidence</td>
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<td>370,000</td>
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<td>Dialysis prevalence</td>
<td>136</td>
<td>190,000</td>
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Table 7.3. Validation results for type 1 and type 2 diabetes mellitus.
7.5. DISCUSSION

The objective of the guideline formulation project in the Netherlands is to enhance appropriate clinical decision-making and better-informed priority setting in resource allocation at various levels in health care management. The project is a common effort from (para)medical experts, patient representatives, health care financiers and research institutes and was started in January 1998. Development of guidelines to prevent diabetes nephropathy is one of the first topics to have been covered. Cost-effectiveness calculations of proposed treatment measures did not give any reason for changing guideline proposals on prevention of diabetes nephropathy. A combined effort to incorporate data on cost-effectiveness early in the guideline development process has resulted in an evidence based and transparent guideline with explicit information on costs and effects. An alliance and a common body of knowledge have been created which will serve future health care policy-making. The final version of the guideline will get a supplement on the performed cost-effectiveness analysis.

Using cost–effectiveness analysis as a tool in health care policy and decision-making, requires results that are comparable across interventions. As a standard measure of effect we used quality adjusted life years (QALY’s), which were calculated using international data on utilities for ESRD i.e. 0.61 (DCCT, 1996). For the other disease states no uniform utilities, other than 1.00 could be found. Costs and benefits of a health intervention occur at different points in time. For treatment measures to prevent diabetes nephropathy, the costs will precede the effects. Calculating present values of both costs and effects of a health intervention, by discounting costs and effects, is another step in standardizing results and enabling policy makers to make an objective comparison between different interventions, with different time lags between costs and effects. Discount rates were based on expected economic growth in the Netherlands and future elasticity in the social utility function (Gold et al., 1996). A discount rate of 3% on both costs and effects was used in this study. From a health economic point of view, a cost-effectiveness analysis using a societal perspective would be more complete. From a practical point of view, the analysis has to be timely and within the budget set for the guideline development project. In this study, the health care costs of renal replacement therapy in elderly diabetes patients largely influence the cost-effectiveness ratio. Indirect costs and effects are unlikely to change the cost-effectiveness ratio significantly. To serve the goal of developing an evidence-based, transparent guideline with data on cost and effects, a health care perspective was considered sufficient by all involved.

Validation of the model was done, using national diabetes prevalence and incidence data, and comparing model outcome with empirical data on dialysis prevalence from the Netherlands. Dialysis prevalence calculated by the model is somewhat different from prevalence data in the dialysis register. One explanation for the discrepancy in both type 1 and type 2 diabetes is the absence of a historical time dimension in the Markov–model. To calculate ESRD prevalence for 1994, we would have to use diabetes incidence data from some decades ago. These data are not available since accurate registration is from 1980 onwards. Diabetes incidence in the past however, will be lower than the 1994 incidence figures, as diabetes incidence in the Netherlands has shown an annual increase of 1-3% (Ruwaard, 1996). Using diabetes prevalence data to calculate ESRD prevalence
Diabetes morbidity ignores the historical time dimension. For type 1 diabetes, the model produces dialysis prevalence figures resembling actual dialysis prevalence data, when diabetes prevalence data are used. For type 2 diabetes, dialysis incidence calculated by the model is somewhat higher. This can partially be explained by an underestimation of actual ESRD prevalence by the national dialysis register (Renine, 1998). Elderly diabetes patients developing renal failure often do not start dialysis. We constructed a model that is consistent with existing Dutch data on diabetes. Additional calibration we consider unnecessary. Most likely, the assumption that no patients are taking ACE-inhibitors is not correct. There are no data available yet on over- and under-prescribing of this recommended drug. On the whole, the Markov model does offer a valid tool to draw conclusions on incremental costs and effects of guideline treatment over current anti-diabetic treatment.

Conclusion
Guideline measures on prevention of diabetic nephropathy are considered cost–effective for both type 1 and type 2 diabetes. Intensive blood glucose control is cost-effective whereas the use of ACE-inhibitors in macro-albuminuria is cost saving. When we take into account that intensive blood glucose control has effect on other diabetes complications (neuropathy and retinopathy) as well, intensive treatment will resort in more effects and become even more cost–effective. Evidence-based guidelines, formulated in a standardized way with a simultaneous cost–effectiveness analysis, will enable various stakeholders at different levels in health care policy making and decision making, to come to better informed decisions and resource utilization. Development of the diabetes nephropathy guideline with a concomitant cost-effectiveness analysis has brought health care providers and health services researchers in the Netherlands together.
Chapter 7

REFERENCES

8. Casparie AF (1999): The costs of efficiency in health care - the example of diabetes guidelines, Medisch Contact 54 1129-33. [Dutch]
### Chapter 7

**APPENDIX**

<table>
<thead>
<tr>
<th>state transition no</th>
<th>description of state transitions</th>
<th>diabetes type 1</th>
<th>diabetes type 2</th>
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<td></td>
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<td>annual transition probability</td>
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<td></td>
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<td></td>
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<td>3-5yrs</td>
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<td></td>
<td></td>
<td>later yrs</td>
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<tr>
<td>3</td>
<td>macroalbuminuria to ESRD</td>
<td>1st yr</td>
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</tr>
<tr>
<td></td>
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</tr>
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<td></td>
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<td>&gt;4 yrs</td>
<td>0.0119</td>
</tr>
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</tr>
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<td></td>
<td>albuminuria</td>
<td>later yrs³</td>
<td>*1.07^(t)</td>
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<td>annual mortality rate micro-</td>
<td>1st yr</td>
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<td>albuminuria.</td>
<td>later yrs</td>
<td>*1.07^(t)</td>
</tr>
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</tr>
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<td>albuminuria.</td>
<td>later yrs</td>
<td>*1.07^(t)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1st yr</td>
<td>0.2000</td>
</tr>
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Table. State transition probabilities in the models for type 1 and type 2 diabetes nephropathy.

¹ (HbA1c type 1 diabetes / 9.0%) ^ ß. ²(HbA1c type 2 diabetes / 10%) ^ ß

ß is 3.25 for the unconditioned transition rate from normo– to micro–albuminuria and 7.95 for the conditioned transition rate from micro– to macro–albuminuria.

³ annual increase in mortality by ageing: mortality rate first year * 1.07^(time)
CHAPTER 8

LIFETIME HEALTH EFFECTS AND COSTS OF DIABETES

8.1. SUMMARY

Introduction The previous chapter examined diabetes control and treatment in one diabetes complication. Next, this chapter presents cost-effectiveness analyses of interventions for all major complications, using many disease states. The interventions are according Dutch guidelines for diabetes type 2 patients in primary and secondary care. For each type of care, it considers two types of interventions: diabetes control and the preventive treatment of complications, each at current care level and according to the guidelines.

Methods A probabilistic disease history model describes diabetes and its complications over a lifetime, computing quality-adjusted life years and medical costs. It is validated against empirical national figures. Data on the effectiveness and costs of diabetes interventions are from observational current care studies and intensive care experiments. Eighteen intervention mixes are compared to a baseline of 10% HbA1c glycemic control. A stochastic league table defines optimum expansion pathways, starting with the least costly and most cost-effective intervention mix.

Results The interventions may reduce the cumulative incidence of blindness, lower-extremity amputation, and end-stage renal disease by >70% in primary care and >60% in secondary care. All primary care guidelines together add 0.8 quality adjusted life year per lifetime.

Conclusion If few resources are available, treating complications according to guidelines yields most health benefits. Current care of diabetes complications is inefficient. If more resources are available countries may implement all guidelines, also on diabetes control and improve efficiency.
Chapter 8
8.2. INTRODUCTION

Ageing, life style changes and improved case finding will increase the number of diabetes type 2 patients in most societies in the near future (King, 1998). In the Dutch population, diabetes led to a loss of 87,000 disability-adjusted life years in the year 1996, ranking 10th of all diseases (Melse et al., 1998). Diabetes contributes to the occurrence of cardiovascular disease, loss of vision and blindness, kidney failure, disorders of peripheral circulation and loss of sensitivity and pain in the legs, both leading to lower extremity ulcers and amputation. It is the largest cause of blindness in developed countries. About 15% of the dialysis patients in the Netherlands have diabetic nephropathy. In the United States, probably due to less diabetes control, this is 30% (Os van et al., 2000). Lower extremity amputation (LEA) is about 15 times more frequent among diabetes patients than in the general population (Houtum, 1998; Holstein et al., 2000). Health care costs related to diabetes and its complications are high in affluent societies and account for 2.5% of the Dutch medical expenditures in 1996 in the Netherlands (Os van et al, 2000). Cost-effectiveness analyses of diabetes guidelines are relevant for clinical and health policy reasons. Long-term clinical follow-up studies demonstrated that intensive control of blood glucose is effective in reducing the risk of severe diabetes complications (UKPDS, 1998). Health economic studies showed that intensive treatment might lead to lower health care costs, especially through fewer institutional episodes (Klonoff and Schwartz, 2000). Such studies typically report the costs and effects of an intervention given an existing level of control and treatment and hence are context-specific. It is of health policy interest to have more general information on allocation options in diabetes care given the various prevention and treatment options for complications (Gulliford, 1997; Niessen et al., 2000). The premise of such analyses is that, for any given level of resources available, one wishes to maximise the total aggregate health benefits (Weinstein and Stason, 1977; Granata and Hillman, 1998; Murray et al., 2000). A comparison of health effects and costs of optional intervention mixes against a baseline care level facilitates priority setting at varying resource levels. One may consider the efficiency of current interventions (Murray et al., 2000; Hutubessy et al., 2001). In this chapter, a low diabetes control level of 10% glycosylated haemoglobin (HbA1c) is taken as baseline.

In the Dutch setting, primary care physicians are the gatekeepers for secondary care facilities. About 80% of type 2 diabetes patients are treated in primary care and are referred only temporarily for secondary care consultation e.g. for eye screening (Rutten et al., 2001). Specialists in ambulatory secondary settings only treat the more difficult cases. This chapter presents analyses for combinations of various intervention mixes as formulated in the Dutch guidelines for diabetes type 2 care (Ballegooie and Everdingen, 2000; NHG, 1999; Niessen and Casparie, 2001) and reports the allocative options at different resource levels. We consider two sets of intervention mixes for diabetes patients: one for those in primary care and one for those in secondary care.
Chapter 8

8.3. MODEL DESCRIPTION AND SCENARIO DATA

We estimate health effects and medical costs of current care and care according to guidelines in the two groups compared to a baseline setting. We collected data on current care and used data on two experimental guidelines settings (Smith et al., 1999; Sonnaville et al., 1997). We first summarise the applied disease history model for diabetes. Then, we describe the computations to arrive at validated baseline estimates. Last, to obtain comparable cost-effectiveness results, we give the details on the input values for the effectiveness and costs for the two sets of, in total, eight possible intervention mixes for each set.

Multi-state disease model

We modified a probabilistic Markov model to describe the Dutch diabetes situation. It describes the disease history of type 2 diabetes and calculates quality-adjusted life years (QALYs) lived with diabetes and its complications, as well as lifetime medical costs (Eastman, 1997). We refer for detailed description to the original publication. Figure 8.1 summarises the model. It computes the occurrence of the mild and severe long-term diabetic complications and the excess mortality due to diabetes. The model distinguishes five health states for retinopathy, four for nephropathy and three for neuropathy. Patients may progress from states without specific complications, through less severe intermediate stages, towards three severe diabetes complications, leading to severe vision loss (< 20/100), kidney failure or lower extremity amputation. The intermediate retinopathy states are background retinopathy, macula oedema, and proliferative retinopathy. For nephropathy these are microalbuminuria and gross albuminuria, leading to end-stage renal disease (ESRD). The neuropathy complications are leg and foot ulcers and LEA as results from ‘diabetic foot’.

The model describes cohorts of diagnosed diabetes patients. They enter the model one by one through stratified random sampling until a stabilisation of results occurs. It accounts for their age and sex distributions and the distribution of their HbA1c levels (Table 8.1). The complication probabilities are specific for age, gender, and diabetes duration. There are two independent mortality risks. One accounts for diabetes specific mortality and the other for the excess mortality. The latter includes the excess cardiovascular mortality risk. Figure 8.1 indicates that progression towards severe states depends on both the level of diabetes control and the level of specific treatment during the less severe intermediate stages.

Baseline estimates

We applied the disease model to compute a baseline situation (see Table 8.1). HbA1c indicates the level of diabetes control and it is directly related to the occurrence of complicating events later in life (UKPDS, 1998; Eastman, 1997). We used this observed relation to simulate a situation of very low diabetes control. We assumed a HbA1c level of 10% to estimate a baseline incidence of severe complications as this has been used in the original model version (Eastman, 1997). This level of control compares to the Dutch level of control observed about 15 years ago in comparable groups of patients.
Figure 8.1. Overview of groups of disease states in the diabetes model and action effects of intervention mixes. The actual number of possible disease states is higher (see text). a

(Verhoeven et al., 1991). The present average control level is below 8% HbA1c. We did not alter the baseline incidence figures for severe complications but did use Dutch mortality risk estimates. We multiplied the gender and age-specific national mortality figures for 1990 by the increased hazard ratios for Dutch diabetics. An incidence-prevalence-mortality model, used to compute consistent values for each of its three components, estimates at a hazard ratio of 1.55 for mortality for diabetic men and 2.27 for women as compared to the general population (CBS, 1992; Hoogenveen, 2000). The ESRD case fatality rates are also based on national figures (Os van et al., 2000).

Next, we validated model outputs, comparing model output data with empirical data from other sources. The model calculates a baseline life expectancy at age 65 for non-diabetic men of 14.0 and women of 18.6 years. The empirical figures are 14.1 and 18.6 (CBS, 1992). Computed baseline life expectancies for diabetic men and women are 11.3 and 14.9 years. These figures compare well with the (rough) historical estimates of 11.4 and 15.2 (Ruwgaard, 1996). We also compared model outcomes with the national registry figures for diabetes as well as neuropathy and nephropathy complications. This was not possible for retinopathy, due to lack of data. We found only minor differences, which we explain by the lack of an, increasing, incidence trend, underestimation in the registries and varying diagnostic criteria. We concluded that our model values are consistent with available empirical national data on diabetes occurrence (Os van et al., 2000).

Last, we introduced utility weights to adjust the computed life years. We found a single weight of 0.75 for diabetes with or without mild complications based in our EuroQol survey (Redekop et al., 2002b). The utility weight for blindness / low vision is 0.69, for ESRD 0.61 and for LEA 0.59 (Os van et al., 2000; Eastman et al, 1997; Tangelder et al., 1999).
Input data for two sets of intervention mixes

We collected data for the two types of intervention sets (diabetes control and treatment of complications) for each of the two patient groups. (Table 8.1) The difference between the primary and secondary care group is that in the latter diabetes control is more difficult and severe complications are more frequent. Both conditions are indications for a referral according to guidelines (NHG, 1999). Both types of interventions are considered at two different levels of care i.e. current care and care according to recent guidelines (Ballegooie en Everdingen, 2000; Niessen and Casparie, 2001). The guidelines for diabetes control aim at lower levels of HbA1c and the guidelines for complications recommend frequent screening and preventive treatment through laser coagulation, ACE-inhibitors, and foot clinic visits.

So, the first group consists of primary care patients receiving current care interventions (P.CC) or receiving intervention mixes according to guidelines (P.GC). The second group consists of secondary care patients receiving current level of specialist interventions (S.CC) or receiving intervention mixes according to guidelines (S.GC). Each of four different intervention mixes distinguishes two components: diabetes control (P1 or S1) and treatment of complications (P2 or S2). Table 8.1 lists the input values for diabetes control and treatment of complications by patient group and by level of care. This leads to two sets of four single (P1, P2 or S1, S2) and four combined (P1+P2 or S1+S2) mutually exclusive intervention options at current and guideline care level. For instance, the single option P1.CC means diabetes control as currently given and no treatment of complications in primary care. In total, we analyse sixteen of those options of diabetes interventions. (Table 8.2 and 8.3)

Effectiveness diabetes control

Empirical data regarding the level of diabetes control in current and guideline settings (P1.CC, P1.GC, S1.CC and S1.GC) have been collected in three studies (Smith et al., 1999; Sonnaville et al., 1997; Dijkstra et al., 2000). The HbA1c figures for primary care patients (P1.CC and P1.GC) are based on a two-year follow-up of 459 patients in 22 primary care practices (Sonnaville et al., 1997). Effectiveness figures for current secondary care patients are from a survey in 10 general hospitals among 929 patients. [29] Accounting for control effectiveness (versus trial efficacy) we entered the observed distributions of all HbA1c values into the probabilistic calculations instead of the observed means. Table 8.1 shows the HbA1c fractions for those values > 8.5% and for those between 7.0 and 8.5%. It indicates, for example, that in all four groups more than 10% of the patients remains above the 8.5% HbA1c level.

The relationship between HbA1c level and progression to diabetic complications is estimated by a function reported earlier (Eastman et al., 1997). It has been validated for the Netherlands (Os van et al, 2000) and is based on the formula (\((HbA1c / 10) ^ \beta\)). The calculated fraction is the reduction of the transition probabilities towards each of the three complication categories. The \(\beta\) - coefficients are specific for each type of less severe complication. [Eastman et al., 1997] The function shows diminishing returns when lowering HbA1c level through more intensive diabetes control. The UKPDS study confirms the degree of diminishing returns (Stratton et al, 2000).
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients in survey</td>
<td>1,371</td>
<td>459</td>
<td>929</td>
<td>1029</td>
</tr>
<tr>
<td>Mean age (S.D.)</td>
<td>65.2 (11.7)</td>
<td>66.1 (12.5)</td>
<td>69.2 (11.5)</td>
<td>69.2 (11.5)</td>
</tr>
<tr>
<td>Gender distribution (% men)</td>
<td>49</td>
<td>39</td>
<td>43</td>
<td>41</td>
</tr>
</tbody>
</table>

### Diabetes control (P1 and S1)

#### Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average HbA1c % (S.D.)</td>
<td>7.6 (1.5)</td>
<td>7.0 (1.3)</td>
<td>7.8 (1.5)</td>
<td>7.2 (1.3)</td>
</tr>
<tr>
<td>Fraction of patients &lt; 7.0%</td>
<td>0.44</td>
<td>0.54</td>
<td>0.25</td>
<td>0.35</td>
</tr>
<tr>
<td>Fraction of patients &gt; 8.5%</td>
<td>0.28</td>
<td>0.12</td>
<td>0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>Fraction of insulin patients</td>
<td>0.04</td>
<td>0.16</td>
<td>0.74</td>
<td>0.85</td>
</tr>
</tbody>
</table>

#### Medical costs

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits general practitioner</td>
<td>128</td>
<td>318</td>
<td>128</td>
<td>318</td>
</tr>
<tr>
<td>Visits various diabetes specialists</td>
<td>144</td>
<td>120</td>
<td>212</td>
<td>298</td>
</tr>
<tr>
<td>Visits diabetes nurses</td>
<td>63</td>
<td>218</td>
<td>109</td>
<td>218</td>
</tr>
<tr>
<td>Visits paramedics</td>
<td>0</td>
<td>184</td>
<td>48</td>
<td>120</td>
</tr>
<tr>
<td>Oral drug, insulin; self control</td>
<td>347</td>
<td>386</td>
<td>977</td>
<td>1,937</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>40</td>
<td>187</td>
<td>40</td>
<td>271</td>
</tr>
</tbody>
</table>

### Treatment less severe complications (P2 and S2)

#### Effectiveness (probability reduction)

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser coagulation in ME, postponing blindness / low vision</td>
<td>0.05</td>
<td>0.03</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Laser coagulation in PDR, postponing blindness / low vision</td>
<td>0.08</td>
<td>0.015</td>
<td>0.08</td>
<td>0.015</td>
</tr>
<tr>
<td>ACE-inhibitors in gross albuminuria</td>
<td>0.08</td>
<td>0.05</td>
<td>0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>Foot clinic treatment neuropathy</td>
<td>0.17</td>
<td>0.05</td>
<td>0.25</td>
<td>0.05</td>
</tr>
</tbody>
</table>

#### Medical costs

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye screening visit</td>
<td>27</td>
<td>55</td>
<td>27</td>
<td>55</td>
</tr>
<tr>
<td>Laser coagulation + follow-up</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>20</td>
<td>58</td>
<td>20</td>
<td>29</td>
</tr>
</tbody>
</table>

### Treatment severe complications

#### Medical costs

<table>
<thead>
<tr>
<th></th>
<th>(P1.CC+P2.CC)</th>
<th>(P1.GC+P2.GC)</th>
<th>(S1.CC+S2.CC)</th>
<th>(S1.GC+S2.GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blindness</td>
<td>1,200</td>
<td>2,550</td>
<td>660</td>
<td>3,200</td>
</tr>
<tr>
<td>End-stage renal disease*</td>
<td></td>
<td></td>
<td>46,700</td>
<td></td>
</tr>
<tr>
<td>Diabetic foot ulcer**</td>
<td></td>
<td></td>
<td>563</td>
<td></td>
</tr>
<tr>
<td>LEA event / amputation status</td>
<td></td>
<td></td>
<td>12,000/450</td>
<td></td>
</tr>
</tbody>
</table>

Table 8.1. Model input values for diabetes control and preventive treatment of complications by patient group characteristics, effectiveness and annualised medical costs (1996€).

*P* = primary care; *S* = secondary care; ‘1’ = diabetes control; ‘2’ = care of complications; ‘CC’ = current care; ‘GC’ = guideline care. * Weighted average of hemo-dialysis, peritoneal dialysis, home dialysis and transplantation; ** weighted average of ambulatory and in-hospital treatment. ME = macula oedema. PDR = proliferative diabetic retinopathy. LEA = lower extremity amputation.

Sources: (Niessen and Casparie, 2001; Smith et al., 1999; Sonnaville et al., 10097; Dijkstra et al., 2000; Redekop et al., 2001a).
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Effectiveness preventive treatment of complications The effectiveness figures for the treatment of retinopathy and nephropathy are from experimental trials and have been reported before [3, 22] In macula oedema, laser coagulation slows down progression to a vision < 20% at a hazard ratio of 1.17. In proliferative retinopathy, the hazard ratio is 1.71. Data on the effectiveness of the prevention and treatment of diabetic foot are scarce, especially on lowering amputation rates. The Saint Vincent declaration states as the attainable goal a 50% reduction. A Dutch study and others report some supportive evidence for this, relatively pessimistic, estimate. We applied hazard ratio to the amputation transition probability of 3.72 for primary care patients and for 2.41 in secondary care patients. Table 8.1 lists the resulting changes in probabilities. Unless stated otherwise, we present these three types of specific preventive treatments combined as one intervention mix. We distinguish one for current care (P2.CC and S2.CC) and for guideline care (P2.GC and S2.GC).

Health care costs by intervention mix We collected data regarding health care utilisation from the same three studies and did a large cross-sectional study of primary care patients. This study reports the actual health utilisation and costs from 29 general practices of 1371 primary care patients. Health utilisation estimates for current secondary care are from a hospital survey (Dijkstra et al., 2000). The cost estimates for the implementation of guideline care are from two experimental studies applying intensive treatment protocols in primary and secondary care patients (Smith et al., 1999; Sonnaville et al., 1997).

Table 8.1 lists the cost input values for diabetes control and treatment for the four categories of patients (P.CC, P.GC, S.CC, and S.GC). Medical costs of amputation, follow-up after amputation, end-stage renal disease, and blindness are assumed the same in all four patient groups. The calculated lifetime cost estimates do not include the medical costs of non-diabetes-specific conditions. We provide more cost details in the Dutch report (Niessen and Casparie, 2001).

8.4. RESULTS

We computed lifetime health effects and medical costs for the sixteen diabetes intervention mixes in the two sets. One set included all possible mutual exclusive intervention mixes for primary care (P) and the other (S) includes all possible mutual exclusive mixes for secondary care. We first present the specific health effects for the eight single components of the intervention mixes (P1, P2, S1, S2) for current care and guideline care (CC and GC). Next, we present effects and costs of the eight single components and eight combined mixes for control and preventive treatment (P1+P2 en S1+S2). This leads to results for in total sixteen intervention mixes as listed in Table 8.2. Last, we account for the uncertainties in making the optimal allocative choice from the two sets of eight mixes in a stochastic league table.

Health effects Table 8.2 shows the incidence of complications for patients under the four intervention mixes (P.CC, P.GC, S.CC, and S.GC). It compares the effects of each single component i.e. diabetes control (P1 or S1) and preventive treatment of complications (P2 or S2) to the baseline estimates. The first column gives the results of the baseline
Diabetes care scenario. Diabetes control reduces the incidence of all complications. Once less severe complications occur, preventive treatment reduces progression to severe complications. Some 74% of type 2 diabetes patients developed background retinopathy under the baseline scenario, whereas blindness occurs in 13.5%. Under current level of control, this is reduced with more than 75%. Implementation of control guidelines among primary care patients reduces the cumulative incidence of blindness by more than 90%, whereas ESRD falls with 67% from 5.6% to less than 0.5%. The cumulative incidence of diabetes-related amputations decreases from 7.7% in the baseline to 2.1% in the current primary care setting. Similar, less substantial declines take place among the more complex patients in ambulatory secondary care. Implementation of secondary care guidelines leads to a reduction of blindness with 29%, of ESRD with 62%, and of LEAs with about 27%. Table 8.2 shows also that the incidence of these severe complications results in more patients with less severe complications in the case of blindness (P2.GC and S2.GC) and amputations (S2.GC). This leads to a relative increase in costs. Reductions due to specific single treatments of complications (not listed) are substantial, but lower. Patients in current care with higher initial HbA1c-level benefit more from guideline control than those with lower initial values of HbA1c.

Table 8.2. Lifetime cumulative incidence (%) of diabetes complications by intervention mix component

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>P1.CC</th>
<th>P2.CC</th>
<th>P1.GC</th>
<th>P2.GC</th>
<th>S1.CC</th>
<th>S2.CC</th>
<th>S1.GC</th>
<th>S2.GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background retinopathy</td>
<td>73.6</td>
<td>17.9</td>
<td>69.7</td>
<td>8.4</td>
<td>68.9</td>
<td>32.2</td>
<td>70.3</td>
<td>24.8</td>
</tr>
<tr>
<td>Macular oedema</td>
<td>38.5</td>
<td>7.2</td>
<td>36.0</td>
<td>3.3</td>
<td>35.9</td>
<td>12.9</td>
<td>34.3</td>
<td>9.1</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>8.7</td>
<td>1.2</td>
<td>8.6</td>
<td>0.5</td>
<td>9.4</td>
<td>1.0</td>
<td>7.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Low vision / blindness</td>
<td>13.5</td>
<td>2.5</td>
<td>9.1</td>
<td>1.0</td>
<td>8.1</td>
<td>4.1</td>
<td>7.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Micro-albuminuria</td>
<td>36.4</td>
<td>15.2</td>
<td>30.5</td>
<td>12.0</td>
<td>30.1</td>
<td>22.9</td>
<td>33.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Macro-albuminuria</td>
<td>25.2</td>
<td>4.4</td>
<td>20.0</td>
<td>1.7</td>
<td>19.8</td>
<td>5.6</td>
<td>22.2</td>
<td>2.3</td>
</tr>
<tr>
<td>ESRD</td>
<td>5.6</td>
<td>0.9</td>
<td>4.1</td>
<td>0.3</td>
<td>2.5</td>
<td>1.1</td>
<td>2.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>19.7</td>
<td>6.3</td>
<td>17.6</td>
<td>3.3</td>
<td>17.3</td>
<td>8.8</td>
<td>18.1</td>
<td>6.5</td>
</tr>
<tr>
<td>LEA</td>
<td>7.7</td>
<td>2.1</td>
<td>5.7</td>
<td>1.2</td>
<td>4.0</td>
<td>3.0</td>
<td>5.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Table 8.2. Lifetime cumulative incidence (%) of diabetes complications by intervention mix component

*P*= primary care; *S*= secondary care; *1*= diabetes control; *2*= care of complications; *CC*= current care; *GC*= guideline care.

Costs-effectiveness of diabetes interventions Figure 8.2. and Table 8.3 present the means of the computed QALYs lived and the discounted additional lifetime costs per average diabetes patient for the 16 possible combinations of the four intervention mixes (P.CC, P.GC, S.CC, and S.GC). The standard deviations for the QALYs lived vary between 5.04 and 6.01 years and for the lifetime costs between 3,103 and 8,265 euros. The calculated baseline life expectancy is 9.29 QALYs (SD=5.3). The SD value compares well with observed figures for the unadjusted life expectancy (CBS, 1992). The large SDs for lifetime costs are due to the large variation in remaining life years lived and the less frequent occurrence of the most costly complications. This reflects clinical reality in the treatment of older individual patients: given the high individual risks of dying from other causes, future health benefits and medical costs are uncertain at the individual level. The higher costs of guideline control (Table 8.1) and the treatment costs of complications are partially offset by reductions in the costs of severe complications, especially by savings on the care of severe renal and lower extremity complications. All primary care
guideline interventions together (P1.GC+P2.GC) show the highest health yield for a single intervention set: about 0.8 QALY per average lifetime. As a single intervention, eye screening and laser coagulation (not listed) fall within the same range of cost-effectiveness. The cost-effectiveness ratios for current treatment for renal and lower extremity complications (not listed), as single interventions, are much less cost-effective. Diabetes control in secondary care patients is still more costly per unit HbA1c reduction. This explains why primary control is more cost-effective than specialists’ control. As the current control level is already high in both primary and secondary care, even more tight control shows increasing costs and diminishing returns.

The two guidelines intervention mixes for complications (P2.GC and S2.GC) are dominant compared to the current care of complications (P2.CC and S2.CC). Guideline treatment of complications (P2.GC and S2.GC) is cost-effective for three reasons: the intervention costs are low, the effects are immediate in a large majority of patients, and the indicated patient subgroup is relatively small. In diabetes control, annual costs are higher, health gains occur later in life, and many patients need to be treated to prevent relatively few, severe and costly complications. Therefore, current control is less cost-effective than preventive treatment of complications. Intensive control is even less cost-effective.

Figure 8.2. The cost-effectiveness plane: QALYs lived and lifetime medical cost (3% discounted) for each intervention mix, the baseline value and combinations of P and S mixes.

‘P’= primary care; ‘S’= secondary care; ‘1’=diabetes control; ‘2’=care of complications; ‘CC’= current care; ‘GC’= guideline care.
### Table 8.3. QALYs lived and medical costs (1996€) per average remaining diabetic lifetime for the two independent sets P and S of intervention mixes, ordered by QALYs lived.

<table>
<thead>
<tr>
<th>Intervention mixes</th>
<th>Model outputs</th>
<th>Cost-effectiveness results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QALYs lived</td>
<td>Lifetime costs</td>
</tr>
<tr>
<td>No</td>
<td>Single set mixes</td>
<td>No</td>
</tr>
<tr>
<td>0</td>
<td>Baseline care</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>S2CC</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>S1.CC</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>S2.GC</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>S1.GC+S2.CC</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>S1.CC+S2.CC</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>S1.CC+S2.GC</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>S1.GC</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>S1.GC+S2.GC</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>P2.CC</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>P2.GC</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>P1.CC</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>P1.CC+P2.CC</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>P1.CC+P2.GC</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>P1.GC+P2.CC</td>
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</tr>
<tr>
<td>15</td>
<td>P1.GC</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>P1.GC+P2.GC</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>P2.GC+S2.GC</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Ibid+S1.CC</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Ibid+P1.GC</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Ibid+P1.GC+S1.CC</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Ibid+P1.GC+S1.GC</td>
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</tr>
<tr>
<td>22</td>
<td>Ibid+P1GC</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Ibid+P1GC</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Ibid+P1GC+S1.CC</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Ibid+P1GC+S1.GC</td>
<td></td>
</tr>
</tbody>
</table>

Table 8.3 and Figure 8.2 indicate one possible optimal resource expansion option i.e. how to prioritise implementation of efficient diabetes care starting from a baseline level. Here, one would start by choosing the most cost-effective option at the lowest budget needed, followed by the next cost-effective etc until resources are exhausted (Weinstein and Stason, 1977). In Table 8.3, only the relevant combinations of P and S are listed (no 17-25). Other combinations are possible but not relevant for the path. For the sets of mutual inclusive interventions (P and S) the order would be to start with the guidelines treatment for complications, next to add primary control, and last to implement intensive secondary control. The optimum expansion path for all combinations of all possible P and S mixes starts with S2.CC. This is the most efficient and least expensive option i.e. gives most...
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savings, compared to baseline level (Table 8.3). The specific implementations steps would
be to improve this to S2.GC, add P2.GC, add P1.CC, improve this to P2.GC, and, last, to
included the remaining S2.GC option. At mid-range budgets also other, single and
combined, mixes are on other expansion frontiers e.g. adding S1.CC after the
implementation of P2.GC and S2.GC. S1.CC (Figure 8.1) can be implemented at much
lower costs, but is three times less cost-efficient, at 21.897 Euro per QALY. At higher
budgets, health effects and the absolute costs for secondary care patients are less
influential due to the relative small size of this group. Health gains in this group, although
very inefficient (Figure 8.2), come for a minimal extra amount per average lifetime. Many
more expansion paths are possible if one takes into account uncertainties e.g. standard
deviations of health effects and lifetime costs. The next section considers all of these
paths together.

8.5. STOCHASTIC LEAGUE TABLE FOR DIABETES CARE

The uncertainties in lifetime cost and health effects for the (combinations of)
intervention mixes are large, especially if compared to the absolute changes in costs and
effects in relation to the baseline (Table 8.3). The reason is primarily, as said, the wide
distribution of overall mortality risks and of risks of complications. Next, they are due to
the wide variation in HbA1c levels as the effects of diabetes control (Table 8.1). When the
budget is less than €300 per lifetime (€20 per year) there will be not enough funds for
even the least expensive and most cost-effective option – preventive treatment of
complications in the high-risk group (S2.CC in Table 8.3). In case of unlimited resources,
all guidelines may be implemented, in spite of the uncertainties and relative inefficiencies.
As most countries are somewhere in between, the optimal allocation for a range of
budgets should be presented.

We used the outcome distributions of lifetime costs and effects for the individual
intervention mixes, generated by our model, in another Monte Carlo simulations. The
point estimates and standard deviations define the distributions (Table 8.3). We made the
common assumptions that costs have a lognormal distribution and health benefits have a
normal distribution and that there is no correlation between costs and effectiveness in
each Monte Carlo replicate. In all iteration we computed the optimal expansion path in
an application of the MCLeague approach, described elsewhere (Hutubessy et al., 2001).
The advantage of this method is that it accounts for uncertainties and, instead of
indicating the one optimal choice, it allows for combinations of packages for independent
groups. We consider the two sets of interventions for primary and secondary care
together but independent. This implies that one can implement one set without
influencing the outcomes and /or costs for the other group of patients. Within each
independent set only one intervention (or none) of all mutually exclusive options is
selected. Depending on the available budget, one intervention from each set can be
included at the same time. Taking all random simulations together, one can calculate the
number of times that a specific intervention would be included in the optimal mix of
interventions at each level of resource availability.
Figure 8.3 shows the probability of inclusion in the optimum set for each intervention mix by available budget level available for the two combined groups (P and S). The computations include only the uncertainties in effectiveness and costs of the interventions. (Table 8.1) We omitted the uncertainties in the risk of dying and getting
complications. At the lowest budget level, the optimum mix is S2.CC for a only very short budget range. Here it is better to implement S2.GC (lower half). The size of the involved patient subgroups is small and costs are low. At somewhat higher budget levels, the optimal mix also includes the guidelines regarding complications for the, small, primary care group (P2.GC). Next, at slightly higher budgets, P1.CC+P2.CC is the better option with a probability of 55%. However, at the large mid-range levels the adoption of primary guideline care of complications (P1.CC+P2.GC) is more likely to be efficient, in combination with guidelines care of the high-risk secondary care patients. Figure 8.3 shows a clear pattern at the highest, developed country, budget levels: the inclusion of intensive diabetes control (P1.GC and S1.GC) is the best option, both as single options or combined with the guidelines for complications. The addition of these latter guidelines (P2.GC and S2.GC) leads to similar probabilities, as these two latter strategies need a lower budget per average lifetime. The pattern for secondary care patients is less certain as compared to primary care. The current primary care options for complications should not be included at all (< 10%).

8.6. DISCUSSION

Our analyses show that the diabetes care guidelines are cost-effective in reducing severe and expensive complications. This reconfirms the results of other studies (Os van et al., 2000; Klonoff and Schwartz, 2000). They also show that implementation of the guidelines for complications both in primary and secondary care reduces the current inefficiencies in diabetes care. In case of low available resources, a combination with moderate diabetes control (P1.CC) is a good option. Also while including uncertainties, the mixes that include guideline treatment of complications continue to be a likely optimum choice. At high resource levels, all primary and secondary care guidelines are relevant. The interventions in secondary care are cost saving compared to baseline; those for primary control cost about 6-7000 Euro per QALY gained.

Cost-effectiveness methodology

The inclusion of a baseline scenario as a reference level is one way to operationalise the generalised CEA approach of the WHO (Weinstein and Stason, 1977). Our baseline scenario represents the average low controlled diabetic still receiving care for severe complications. Estimates for this situation can be relatively well documented as the relationship between HbA1c blood values and the occurrence of complications is well established. The exact natural history of diabetes, giving no treatment at all, however, remains unknown.

The first advantage of our approach is the possibility to assess the relative efficiency of the current mix of care. For the Netherlands data on the level of current diabetes care have become recently available (Redekop et al, 2001a). The present study shows that, due to under-treatment, current primary care of complications is inefficient as more costs due to severe complications can be prevented (Table 8.3). In a direct, context-defined, comparison of current care and guidelines care this would show as cost savings like we
demonstrated elsewhere for diabetes nephropathy (Os van et al., 2000). The comparison with a baseline level makes the information for health policy makers more complete and indicates the level of expenditures still needed.

The second advantage is the possibility to consistently compare intervention mixes for two (or more) different sub-populations at different available budgets after choosing the right denominator. This allows the policy maker to make optimum choices from a league table as is shown in Figure 8.3. In the league table analysis, the unit of analysis is the average cost per diabetic lifetime. Given the small numbers of patients, the provision of secondary care leads to a low average lifetime costs for all diabetics, in spite of high individual costs and higher cost-effectiveness ratio’s. In case of a low budget, preventive treatment of these patients according to this analysis deserves priority. This is only one, utilitarian, way to define optimum net benefit give a fixed health budget to spend for a defined population. QALYs and costs for both groups of patients in our analysis have the same weights and have the same denominator (the average diabetic lifetime).

Different health policy criteria, like equity considerations, might lead to different weights for example priority to the more disabled (Ubel et al., 1999). In this case, the policy maker might choose one of the less likely, nevertheless optimum, options.

There is an indirect interdependence between the health gain and costs due to diabetes control and due to the specific treatment of mild complications. Both reduce severe complications. In a sense, the diabetes health states act as communicating vessels. Better control leads to fewer patients needing preventive treatment of complications. Absence of diabetes control leads to more patients with complications. Treatment of complications in the absence of control leads, on average, to more health gain and higher costs. The disease history model accounts for this interdependence and illustrates it in the single and combined scenario’s results (Table 8.2 and 8.3). This interdependence of preventive and curative interventions holds for many other diseases and needs to be accounted for in similarly analyses in the future.

The baseline estimates are difficult to validate. It might be possible to use a specific calendar as a reference situation, computing ‘backwards’ (Os van et al., 2000). We did this and presented some historical evidence. Our baseline quality-adjusted life expectancy of 9.3 QALYs due to low diabetes control is probably an overestimation. At a mean 10% HbA1c level, there will be loss of health due to direct metabolic complications, leading to less QALYs and higher costs in the baseline scenario. This would lead to more favourable cost-effectiveness ratios for the intervention sets. Certainly within limits, it doesn’t make an essential difference which baseline is chosen as long its health effect values are substantially lower than the computed gains for the actual interventions.

Our main conclusions on the optimum mixes, however, are based on the relative values for health benefits and costs of the studied intervention mixes, starting with the optimum choice at the lowest budget level. This does not change in case of different baseline values, not would the relative values for the interventions change. Figure 8.3 would not change and lead to the same overall conclusions. A comparison with interventions for other diseases to compute the net population benefit, however, would need redefining the baseline values to include the characteristics of the involved other patient (or population or high risk) groups. Uncertainties in other model input values, such as those for discounting, utility weights or transition probabilities do not change the set of relative values substantially either.
Conclusion

In case of low resource availability (< €300 per diabetes lifetime), none of the diabetes mixes is a relevant policy option. Highly likely optimal strategies in resource-poor countries are the implementation of guideline treatment of complications and primary diabetes control (P2.GC, S2.GC, and P2.CC). Our study shows the most likely cost-effective options. However, other allocative criteria will influence the decision-making. In countries with a lot of resources, priority should also be given to the guideline treatment of complications as current diabetes care shows inefficiencies. At budget over €12,000 per diabetes lifetime, one can afford the implementation of all interventions, although at the individual level uncertainties are high.

The implementation results depend very much on the strategies followed (Renders et al., 2001). Simply distribution of guidelines seldom leads to (cost-) effective implementation (Grimshaw et al, 1995; Grol, 1990). Other constraints in a cost-effective implementation are an already high existing level of control and the lack of sufficient improvement in many diabetics. There are diminishing returns in intensive diabetes control. Further selection of high-risk subgroups, by age, sex, risk factor status, and HbA1c level, may lead to the identification of more specific, targeted and cost-effective implementation strategies. For this, it will be necessary to conduct wider-scale and more targeted evaluations of impact and costs of different implementation practices of diabetes guidelines.
18. NHG: (1999); [Dutch College for General Practitioners’ Guidelines Diabetes Mellitus Type 2 - first revision], Huisarts en Wetenschap; 42 (2) 67-83. [Dutch]
Chapter 8

SECTION IV

DISCUSSION
Chapter 9
9.1. SUMMARY

Introduction The multi-state method has been explained and some typical applications have been reported. This chapter examines the policy relevance of the approach. As multi-state models allow for quantification of the health and costs influences of each health determinant, including health interventions, they may facilitate and enhance rational policy making. Broad policy questions in relation to the role of health determinants and health care provision can be specified, modelled and explored like e.g. the use of a zero health expenditure scenarios (chapter 4) and in the use of interventions proposed in guidelines (chapter 5-8). For other broad or detailed policy questions the model approach can be expanded or simplified according depending on the nature of the question. Ethical and political choices will have to remain with the domain of politicians and the public. A lot of the evidence-based approaches, prominent on the national and international agendas for health policy and health research, frequently and increasingly make use of health modelling approaches.

It is unclear what the implications of this policy approach are for the production and distribution of health in populations, given the notion of multiple determinants in health. It is equally unclear what kind of barriers there are to the adoption of evidence-based approaches in health care practice.

Methods Based on an extensive literature review, chapter 9 outlines the ways in which health policy is informed by the results from health research and health modelling. It summarizes approaches in health at three impact levels: inter-sectoral assessment, national health care policy, and evidence-based medicine in everyday practice.

Results Consensus is growing on the role of broad and specific health determinants, including health care, as well as on priority setting based on the burden of diseases. In spite of methodological constraints, there is a demand for intersectoral assessments, especially in health sector reform. Initiators of policy changes in other sectors may be held responsible for providing the evidence related to health. There are limited possibilities for priority setting at the national health care policy level. Hence, there is a decentralisation of responsibilities for resource use towards providers and health insurance companies. They are encouraged to assume agency roles for both patients and society and ask to promote and deliver effective and efficient health care. Governments need to design national frameworks to strengthen their organisation to enhance their roles. The formulation of national health guidelines supported by evidence on effectiveness and efficiency will be one essential element in this process. At all levels multi-state models may play a role as is demonstrated in this book.

Conclusion With the increasing number of advocates for the enhancement of population health in the policy arenas, evidence-based and model-based approaches provide the insights, information, and tools to help with priority setting.
9.2. INTRODUCTION

The multi-state method has been explained and some typical applications have been reported. This chapter examines the policy relevance of the approach. As multi-state models allow for quantification of the health and costs influences of each health determinant, including health interventions, they may facilitate and enhance rational policy making and priority setting. Broad policy questions in relation to the role of health determinants and health care provision can be specified, modelled and explored like e.g. the use of a zero scenarios like for safe water supply and health services (chapter 4) and in the use of preventive and curative interventions proposed in guidelines (chapters 5-8). For other, broad or detailed, policy questions the model approach can be expanded or simplified according depending on the nature of the question. Ethical and political choices will have to remain with the domain of politicians and the public. A lot of the so-called evidence-based approaches are prominent on the national and international agendas for health policy and health research, and make frequently and increasingly use of health modelling approaches. This chapter describes the various areas where the approaches might be used and relates them to the use of the results by health policy makers.

Evidence-based approaches in health can be described as health policy and health care delivery driven by systematically collected proof on the effects of health-related interventions from the social and health sciences. During the nineties, evidence-based approaches have become prominent on the national and international agendas for health policy and health research. Yet, it is unclear what the implications of this rational approach are for the production and distribution of health in populations, given the notion of multiple determinants of health. It is equally unclear what kinds of barriers there are to the adoption of evidence-based approaches in health care practice. Depending on political vision, breadth of causal thinking, and the amount of accumulated evidence on the causes of ill health, health policy addresses health issues at different levels of impact. First, this paper will sketch general developments in the way in which health policy is informed by the results from health research and health modelling. Next, the paper summarises health-modelling approaches in health at three impact levels: intersectoral assessment, national health care policy, and evidence-based medicine in everyday practice.

9.3. INFORMED HEALTH POLICY

Health policy in the broadest sense can be defined as those actions of governments and other actors in society that are aimed at improving the health of populations. Ideally, there would be a cycle of policy formulation, implementation, and assessment. In the assessment of policy outcomes, scientific evidence should play an important role (MOH, 1986; Ruwaard, 1994; Tugwell, 1985; US Congress 1994; McGinnis and Lee, 1995). Over the past two decades, national and international agencies have been systematically collecting a growing body of knowledge in support of health policy (USPHS, 1979; SSH,
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1992; Murray and Lopez, 1996; Ruwaard, 1997; WB, 1993; WHO, 1997; UNEP, 1997). Their documents typically address issues such as the general health status of the population and various subgroups, broad and specific health determinants, the occurrence of specific diseases and the use of health services.

In a rational approach, health policy would address those health determinants and diseases that have a substantial and proven contribution to the health status of the population. The linkage, however, between the evidence in documents and formally stated policy objectives could be stronger (Murray, 1995; Murray and Lopez, 1996; Lerer et al., 1998). In practice, policy decisions are the outcome of complicated political processes among parties with different interests (Stronks et al., 1997).

There are few studies that have assessed the rationale behind national health care expenditures. They suggest that health policies are not necessarily based on research outcomes as they are wrongly targeted or show limited effectiveness. One study reports that high national health care expenditures in Europe may not relate to low mortality levels (Mackenbach, 1991). An older more extensive study allows for inclusion of life style factors and has provided evidence of a more positive link between health care expenditure and low mortality (Wolfe and Gabay, 1987). Another example of policy assessment is the recent analysis by the Institute of Medicine of the National Institute for Health funding for health research (Gross et al., 1999). Their analysis shows a relation between the funding of disease programmes and disease burden when estimated in disability-adjusted life years (DALYs) lost (Gross et al., 1999). However, there is a poor relationship between funding and disease burden when measured in life years lost. This study gives additional examples, by the DALYs criterion, of under-funding, as for perinatal complications and chronic obstructive pulmonary disease, and of relative over-funding as for AIDS and breast cancer. In the three studies, the causality question remains unanswered: does a high disease burden lead to high expenditures or do high expenditures lead to a reduced burden?

In the international debates agreement seems to be growing, regarding the use of a burden of disease approach to select priority areas for policy and research using. In this approach, epidemiology provides the information on the occurrence of specific diseases and the estimated contribution of health determinants to their occurrence (WB, 1993; WHO, 1997a). Simultaneously, health economics can provide information on health equity issues and the selection of cost-effective interventions (Mooney, 1993; Murray, 1994; WHO, 1997b; Drummond, 1997; Elsinga and Rutten, 1997; GFHR, 1999). Priority diseases identified through this approach by the WHO are childhood infections, malaria, tuberculosis, cardiovascular diseases, other tobacco-related diseases, and mental health.

In conclusion, we may state that, given the increasing advocacy for health in the political arena over the past decades, there is an increasing attempt towards transparency and rationalisation of the decision making process in health policy. Consensus is growing on the interpretation of the role of both broad and specific health determinants, including health care provision, as well as on priority setting based on the burden of diseases.
National health status documents recognise the role of multiple determinants of health. It includes the influences of other societal sectors of governmental concern. Research, however, is still scarce. Some econometric modelling deals with entangling the relationship between economic developments, or health care development, and mortality change at the national level (Pritchett, 1997; Kwakani, 1993; Preston, 1975; Mackenbach, 1988; McGuire, 1993). In these kinds of studies, one usually finds some type of ‘health production function’ with determinants such as economic development as measured by GNP, or individual income levels or health care expenditure with diminishing marginal returns and increasing efficiency over time. Given a particular level of economic development and average income, variance in health status is also said to be associated with income distribution by socio-economic group (Kaplan, 1996; Van Doorslaer, 1993).

In these analyses, it is difficult to account for the net effect of changes in the many other direct or intermediate health determinants, although some attempts have been made (Cumper, 1984). More public health orientated studies (Mackenbach, 1988; Wolfe and Gabay, 1987) confirm the important specific contributions of health care in reducing mortality from specific diseases both through prevention and cure. The contribution of health in the increase in productivity has recently been documented and stressed at a macro- and micro-level (WHO, 1997b).

Existing analytic frameworks explaining ill health at the population level (Lalonde, 1974; Vallin, 1992; Frenk, 1993; Ruwaard, 1994; Lerer et al., 1998; WHO, 1997b) consider both broad determinants (such as income, education, nutrition, hygiene) and more specific determinants (such as smoking, hypertension, health care). Recently, the WHO and other UN agencies have recognised the role of environmental determinants of health (Brundtland, 1999; UNEP, 1997). The exact size of the marginal contributions of each health determinant is subject to continuing debate (Weil, 1990, Lerer et al., 1998). There are inputs from epidemiologists, public health specialists, economists, and also demographers (Murray and Lopez, 1997b; Pritchett, 1997; Niessen, 1997; Kwakani, 1993; Mackenbach, 1988; Preston, 1975).

Among the many analytical difficulties are at least three large ones: the measurement of ill health (e.g. in terms of mortality by cause or of reduced quality of life), estimation of the ‘net’ effect of a particular contributing factor and the phenomena of substitution of disease risks. Especially in countries with very low mortality rates, mortality as a outcome measure is insufficient and some measure of quality of life is needed (Murray and Lopez, 1997b). One can use regression analyses estimating the effect of single determinants (Murray and Lopez, 1997a) or use multi-state life tables which account for substitution of disease risks (Barendregt and Bonneux, 1998; Niessen et al., 1997).

Prospective formal appraisal of options in intersectoral and sector-wide health policy is defined as ‘impact assessment’. This has become rather established for policy outcomes other than health, especially in the environmental field (Swart, 1995, Scott-Samuel, 1996). Methods draw on a variety of disciplines and may focus on those groups affected most by policy changes. Scott-Samuel and others argue that health policy makers may make use of the existing experience in developing countries with health impact assessments (Rather et al., 1997; Lerer, 1999). This may be especially useful in relation to health sector reforms.
that are taking place in many countries. Here, a systematic overall approach is still needed (Murray et al., 1995).

We predict that there will be a growing demand for intersectoral assessment, in spite of the fact that its methodology is still developing (Lerer et al., 1998; Rather et al., 1997; Gunning and Hagen, 1987; Mackenbach and Gunning-Schepers, 1997). In the near future, one may see a shift regarding accountability towards the initiator of policy changes in other sectors than health care. They will have to provide evidence on the impact on health of such policy changes. Nevertheless, focus of health policy, until now and probably in the future, is on the organisation of health care provision at the patient level, both in the area of prevention and cure. In the following two sections, we will, first, discuss the use of evidence-based approaches in health care policy at the macrolevel and, next, in health care delivery.

9.5. INFORMED HEALTH CARE POLICY

Several objectives of health care policy are mentioned in policy documents as universal access, comprehensive and uniform benefits, equitable financing, value for money, public accountability, and freedom of choice by consumers and providers (Daniels, 1996). When attempting to support health policy, it is important to understand how these objectives can be defined, operationalised and measured. This is by no means straightforward. At the start of an EC-funded programme on equity in the finance and delivery of health care, Van Doorslaer et al. (1999) studied policy statements concerning these two dimensions of equity in nine European countries. As a second step, they were forced to use their own interpretation to arrive at meaningful operationalisations of those concepts. Furthermore, the interpretation in terms of the policy implications of the redistributive effects of health care finance found in their study, is also tedious (Van Doorslaer et al., 1999). There are also methodological issues raised on how specific interventions can be evaluated. A community intervention trial with some experimental and some control populations may be most desirable, but will be costly (Mackenbach and Gunning-Schepers, 1997). So an important obstacle to evidence based health policy are a clear understanding of policy objectives and the availability of relevant measurement instruments.

In this paper, we have focussed on priorities in health policy and the efficient allocation of resources to population groups (Rutten, 1996). Several approaches are attempted to inform decision-makers at different levels in the health care sector on how to allocate resources (Patrick, 1993; Wang et al., 1999; Murray, 1994; WHO, 1986; NERA, 1993). The WHO review concluded that there has been a lack of understanding and of data to support the modelling needed. At the moment, programme budgeting and marginal analysis (PBMA) is enjoying a revival in the British National Health Service as a means of supporting of decisions on changing resource allocation to groups in the population, which are well defined in terms of having a particular disease or otherwise. Expert groups are often used as a source of information to generate options for resource shifts but critics suggest that these groups lack a shared understanding of current practice and are
inadequately informed about the impact of resource shifts on patient flows and resulting health benefit (Posnett, 1996). Others added that the savings resulting from taking away resources from a programme might only materialise after considerable time and that the transaction costs of resource shifts may be substantial. This is a serious, often overlooked, issue also relevant to economic evaluation in general, which may lead policymakers to doubt the relevance of these approaches. More detailed information such as a diagram of patient flows through the system showing the numbers going through each of the pathways of the diagram, the volumes of care activity and expenditures in each of the pathways, and their impact on health outcomes may inform and facilitate the assessment of resource shifts in PBMA (Posnett and Street, 1996).

Related to PBMA is the determination of topics that should be given priority in evaluation research and consequently be considered for possible resource shifts. This is done at the national level in a number of countries with social health care insurance. In the Netherlands, the Health Insurance Council advises national policy makers on how to improve the efficiency of the system and plays a growing role in the identification of priorities for economic evaluation research (Elsinga and Rutten, 1997). In 1993, a selection of 126 technologies was made by means of a two-round Delphi procedure involving some 30 experts. Recently, this procedure was repeated and improved (Health Insurance Council, 1999). Initially, 800 persons from important health care organisations were asked by questionnaire to suggest topics, this resulting in more than 1400 items for further consideration. After clustering these items, information on costs at the macro-level and on health benefit was collected for the remaining 194 clusters, which was checked by a panel of health service experts. Finally, a panel of experts/policy makers made a final selection in two one-day meetings. Here, the weights of the selection criteria were determined and the information complemented. This resulted in a list of 31 topics that will dominate the research agenda in the Netherlands for the coming years.

Among different disciplines relevant to health services research, health economics plays a prominent role in assisting health policy in general and priority setting in particular. Hurst (1998) considered the impact of health economics on health policy in England and identified a definite impact on the financing and organisation of the National Health Service (NHS), especially regarding the recent reforms and the introduction of new health technologies. Economic evaluation, which is rooted in health economics but has a more multidisciplinary nature, has certainly gained influence. For instance, in most countries public health programmes will not be introduced until careful assessment has taken place in terms of their cost-effectiveness. The same holds true for many curative programmes with large financial consequences. The studies by Buxton (1985) and by Van Hout (1993) on the introduction of heart transplantation and by Ludbrook (DHSS, 1986) and Van der Maas (1989) on breast cancer screening in the U.K. and the Netherlands are classical examples. They have been followed by numerous other studies that also have had substantial impact. For some types of decision-making, economic studies are officially required, both on the central level and at peripheral level (e.g. mandatory investment appraisal in the NHS). An illustration of this is the diffusion of the Australian type system of requiring evidence on cost-effectiveness before listing and/or reimbursement decisions on new pharmaceuticals are made (Langley, 1996). Such systems are going to be introduced in Denmark, Finland, The Netherlands, Portugal, Canada (CCPHTA, 1997) and the UK (Smith, 1999; Freemantle and Mason, 1999).
Managed care programmes in the United States required similar evidence on products from manufacturers, specifying the providers perspective (Langley and Martin, 1997). Furthermore, it is important to assess possible discrepancies between the maximum possible outcome as observed in more or less controlled studies and health benefits as seen in actual practice. Health policy may benefit from the identification of the determinants of shortages in the process of health care. Following Tugwell et al. (1985) a comprehensive assessment was organised by the National Institute of Public Health in the Netherlands (Ruward, 1997) to find evidence on the gap between efficacy and effectiveness. In this study five questions were considered: is there a timely contact with a health care provider?; was there a proper diagnosis?; was the indication appropriate?; was the therapy carried out according to the “state of the art”; and was the patient compliant? For ten indicative diseases, these questions were tentatively answered. A large variation in problems associated with these five successive points in the care process was observed. For diabetes, it was estimated that 50 % of patients requiring treatment had not yet established contact with the health care system, while for depression prescribing insufficiently low dosages of antidepressants was also seen in 50% of the cases. In asthma, patients’ compliance is a major problem, while in patients with heart failure the proper indications for medication are not made. Different programmes targeted at different points in the care process should be initiated and considered in terms of their relative cost-effectiveness in comparison to other options for investment.

We conclude that national health care policy making is increasingly evidence-based. Many governments are supporting agencies for evidence-based health care (Hailey and Menon, 1999). At the same time limitations to priority setting at the political level and insufficient availability of relevant evidence are apparent (Raine, 1998). The former can be seen in many health care systems where politicians tend to deviate from sound evidence-based advice in those cases, where they are asked to withheld certain treatment programs from patients. Public opinion then provides a stronger incentive when manipulated well by pressure groups.

We expect a tendency to shift the responsibility for resource allocation in health care from the central level to peripheral levels, where health care providers are encouraged to assume agency roles for both patients and society and as such to promote and deliver cost-effective health care.

In such settings, health policy deals with organising the national framework to use available evidence on such divers areas as diagnostics (e.g. screening programmes), medical treatment, nursing, and care of patients to its full extent.

In the next sections, we discuss practice guidelines that may support doctors and other medical professionals in those roles.

9.6. EVIDENCE-BASED MEDICINE IN PRACTICE

Clinical guidelines can be defined as systematically developed statements to assist clinicians and patient’s decisions about appropriate health care in specific clinical circumstances. If evidence-based, they may contribute to further defining and improving
the quality of health care delivery (Sackett et al., 1996) and enhance population health (Field, 1990; Burnand, 1999). They may promote resource efficiency by identifying sources of inappropriate use of care and lead to decreased practice variation (Mason et al., 1999; US Congress, 1994; Woolf et al., 1999). The overgrowth of thousands of guidelines at various levels gives reason for doubts about their quality and validity and urges for concerted European or North-American action on standardisation and appraisal mechanisms (Burnand, 1999; Shaneyfelt et al., 1999).

A review of the published evaluations of guidelines in the BMJ (Grimshaw and Russell, 1993) showed that, indeed, guidelines might have positive effects on the care process and on outcome, although there are limitations. Collection of evidence on improved population health is difficult and costly and hence lacking so far. Recently, Eccles and Grimshaw edited a series of articles in the Britisch Medical Journal on clinical guidelines (Woolf et al., 1999). We summarise some of their points and add our own experiences.

Methods used to develop guidelines differ according to the degree of reliance on formal literature reviews, the extent to which expert opinion prevails, the degree to which cost considerations are incorporated, and the process by which the ultimate recommendations are expressed. A shift is observable from recommendations based on experience and opinion (opinion-based) towards reliance on scientific evidence (US Congress, 1994; Shaneyfelt et al., 1999; Shekelle et al., 1999). Legal implications might be limited, as individual practitioners remain responsible for their own decision. It is up to them to follow a guideline or not in the case of a particular patient (Hurwitz, 1999).

Criteria for selecting a clinical problem to be addressed by an ‘evidence’ based guideline are typically: the degree of uncertainty about the best strategy e.g. as measured through practice variation, the clinical burden, the amount of evidence on (cost-) effectiveness, the likelihood of influencing practice, the participation of clinicians and the possibility to reach a consensus. Next, we summarise briefly the development of guidelines in different countries, with reference to the BMJ-series.

United Kingdom Guidelines have been around in the country for years. Royal Colleges, other professional societies, Regional Health Authorities, and the NHS have developed their own versions. In addition, national guidelines are converted to local level to encourage adoption in daily practice.

Local Health Authorities are encouraged to use guidelines as a tool to improve the process of care, improve health outcomes, decrease practice variation, optimise resource allocation, guide contracting by the purchasers and commissioning decisions. The guidelines are derived from consensus conferences or expert opinion. There is a growing interest in the explicit, evidence-based and outcome-based methods (Woolf et al., 1999). There is technical support through the NHS Centre for Reviews and Dissemination, the Research and Development programme, and the UK Cochrane Centre. The new National Institute of Clinical Excellence is adding to the regional processes by appraising new technologies, issuing guidelines and encouraging national audit.

The Netherlands Priority setting in health care has become an issue since the eighties, due to rising health care costs, to increased demand for care, to observed inappropriate care and to ageing of the population. One important way to establish this has been by giving the medical professions a central role in verifying medical effectiveness. Originally, guidelines have been meant to promote quality of care based on consensus. Nowadays,
professional groups develop guidelines that encompass evidence-based state-of-the-art statements based on an analysis of the scientific literature and consensus discussions (Dutch Institute for Health Care Improvement, 1999 and 2000; Van Os and Niessen, 2000). The evaluation of guideline implementation has become a focus of research (Wensing et al., 1998). Collaboration is necessary between all provider groups to secure good communication between different levels of care.

Canada and the United States

In the United States and Canada about 28,000 guidelines have been issued through professional bodies, care institutions, managed care organisations and agencies support by the US Congress (US Congress, 1994). In Canada, evidence-based centres support development and implementation, like at McMaster University. Many guidelines have been systematically reviewed and do not follow standards (Shaneyfelt et al., 1999). The Agency for Health Care Policy, the American Medical Association, and the American Association for Health Plans have established a clearinghouse for guidelines to improve co-ordination. Only recently, one can observe the shift from opinion- to evidence-based guidelines and standardisation, especially at the national professional level. Commercially available guidelines may focus on resource savings. Both insurser and provider groups may use guidelines to influence clinical decision-making. This may result in discussions on who ultimately should decide (Rosenbaum et al., 1999). These discussions tie in with wider discussions on the control mechanisms of regulation and evaluation of clinical practice (Kassirer and Angell, 1998).

Australia/New Zealand

National and state health authorities have developed guidelines since the seventies. In 1995, the Australian Quality of Care and Health Outcomes Committee emphasised the need for evidence-base methods and proposed standardisation. In New Zealand, a government policy committee recommended the use of guidelines to define clinical indications for services rather than endorsing rationing of services by exclusion. The committee produced guidelines on 11 topics. The guidelines on hypertension and cholesterol broke new grounds by linking recommendations to patients’ absolute risk probabilities rather than to generic treatment criteria.

Cost-effectiveness evidence and treatment guidelines

The prominence of evidence-based guidelines coincides with advances within health economics regarding the proper assessment of the cost-effectiveness of health interventions. Economists are emphasising more structured and standardised approaches (Drummond et al., 1997). There is a growing consensus on how to conduct studies at the theoretical level (Gold et al., 1998; Drummond et al., 1997) with the possible exceptions of how to deal appropriately with productivity costs, time preference and uncertainty (Briggs and Sculpher, 1995; Parmigiani et al., 1997). At the practical level, there is still large variation in the actual measurement and valuation of costs and the generalisation of results from a specific research setting. Major journals have made their conditions for publication of cost-effectiveness analyses explicit (Kassirer and Angell, 1994, Drummond and Jefferson, 1996). At the same time, one has concluded that the quality and frequency of papers in general medical journals on cost-effectiveness of interventions are increasing (Udvarhelyi, 1992; Holloway et al., 1999).
Hence, it only seems natural that, in the slipstream of clinical guidelines development based on evidence on effectiveness, demands have become louder to expand the required evidence to include economic information. The increased interest in the economic aspects of clinical guidelines stems from a policy concern about rising health care costs, an ageing populations, increased demand for care, the growth of new treatments and technology and a desire to make the best use of available health resources. The pleas are to be at least cost-conscious and to clarify resource implications (Haycox et al., 1999; Mitchell, 1997; Power and Eisenberg; 1998; Sloan and Grabowski, 1997). In addition to the inherent scarcity of resources, the motives behind these depend on the position of the involved actors in health care (Mason et al., 1999). They relate to cost containment, efficiency in resource use and opportunity costs (health policy makers), or to enhancement of guideline implementation and appropriate financing (clinicians and patient groups).

In pilot settings, both in the Netherlands and in England, participants in consensus meetings include health economists (Borst-Eilers, 1997; Mason et al., 1999). In England, the topics discussed in these meetings are in primary care. Criteria for the selection of topics in the Netherlands have been the involved burden of disease as expressed in DALYs, the involved costs, and the available cost-effectiveness evidence on the topic. In both countries, participants in the consensus meetings do explicitly take into account information regarding the costs of the guidelines as well as their cost-effectiveness. They conduct systematically an assessment of guidelines options along dimensions like effectiveness, health status, safety, accessibility of service, resource use and costs (Mason et al., 1999). The consensus process results in weighed recommendations that may reflect some or all of these dimensions. Previously published cost-effectiveness analyses might be helpful for comparison, still, it is in the nature of the guideline process that new costing and analyses need to be done.

First observations are typically related to combining health economics and guidelines development. They involve both methodological and operational issues. The methodological constraints include the lack of adequate cost data, the lack of effectiveness data to back-up efficacy data from trials, short trial time horizons and the lack of adequate quality of life measures. This increases uncertainties. An extension of the evidence grading system may account for the economic uncertainties (Mason, 1999). E.g. the highest grade for cost data may include those based on actually observed changes in health care consumption. At lower evidence levels of cost-effectiveness, economic evidence would be purely informative and not directive. In concordance with earlier recommendations (Drummond et al., 1997; Gold et al., 1996) also in the guideline process, panellists’ recommendations should be transparent to all involved. They should allow opportunities to alter costs, effectiveness, or utility input data to facilitate local adjustment and acceptance (Mason et al., 1999).

Operational constraints concern the involvement of the whole consensus group, the thorough exploration of effectiveness evidence, presentation of results including uncertainties and the arrival at a general value judgement. It is the Dutch experience so far that consensus can be reached relatively easy when there is published evidence (van Os and Niessen, 2000; Dutch Institute for Health Care Improvement, 2000). An important condition for consistency in the application of cost-effectiveness information is an agreement on the criteria for cost effectiveness. In the Dutch guideline
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on the use of statins for lowering cholesterol in the primary and secondary prevention of cardiovascular disease consensus among medical and economic experts has been reached to use a threshold value for cost-effectiveness of $18,000. (Dutch Institute of Health Care Improvement, 1999). The threshold value has evoked a lot of debate. We expect that more discussion will be needed on acceptable levels of cost effectiveness across guidelines, especially regarding curative versus preventive programmes. Also in our society, the responsibilities of politicians and medical providers need to be defined for setting the standards of care, for determining the societal willingness to pay for health benefits, for deciding on what kind of care patients will receive (Rosenbaum et al., 1999). Ultimately, the quality of the implementation of the guidelines determines their contribution to population health, including of those guidelines that include economic considerations.

**Barriers in implementing evidence-based recommendations**

Well-constructed guidelines may have a substantial impact on quality of care. Focussing on problems of overuse, costs may be reduced in the process. The complete implementation of a guideline should lead to improved health and changes in costs as estimated in the development process. However, the mere existence of a good, evidence-based guideline does not lead automatically to improved efficiency in clinical practice (Feder et al., 1999; Wensing et al., 1998).

The ultimate empirical proof of the effectiveness of the guidelines can only be established when its implementation is properly monitored and evaluated. In the Netherlands, the implementation of a selected number of guidelines for cost-effective health care (Niessen and Casparie, 2000; Dutch Institute for Health Care Improvement, 1999 & 2000) will be monitored. Several factors influence the implementation of a good guideline: individual beliefs, attitude and knowledge of the clinical professionals, local, organizational and economic circumstances, priorities and commitment of the parties involved and the implementation process itself (Wensing et al., 1998; Feder et al., 1999). Consequently, an inventory of these barriers is important in order to optimise the implementation of a guideline. Some practitioners are already working using high standards of care. They will require few incentives to capitalise on the value of guidelines in their efforts to improve. However, others will need additional inducements. Using reimbursement mechanisms to reward the attainment of high quality, publishing data on provider performance on various quality measures and recognising the advantageous effect of attachment to guidelines on liability may provide such incentives.

From our overview, we conclude that, for the present decade, clinical guidelines are there to stay and will continue to play their role in professional training and daily practice. Evidence on effectiveness and efficiency will further strengthen this role. Adaptation to local settings is necessary. During this adaptation process, problems in implementation may become clear and may be solved. Professional groups will be the main actors throughout this whole process, while (local) governments will support the organisation and legal framework.
Consensus is growing on the role of broad and specific health determinants, including health care, as well as on priority setting based on the burden of diseases and the opportunities to reduce such burden in a cost-effective way. There will be a demand for inter-sectoral assessments, in spite of methodological constraints, especially in the area of health sector reform. Initiators of policy changes in other sectors might be held responsible for providing the evidence related to health. Due to limited possibilities for priority setting at the national health care policy level there is a shift of the responsibility for resource use from the central level to peripheral levels. Health care providers are encouraged to assume agency roles for both patients and society and asked to promote and deliver effective and efficient health care. Governments will have to set up the national framework to facilitate their organisation and legal structure to enhance evidence-based health policy. Treatment guidelines supported by evidence on effectiveness and efficiency will be one essential element in this process. At all levels multi-state models may play a role as is demonstrated in this book.

With the increasing number of advocates for the enhancement of population health in the policy arenas (Krieger and Birn, 1998), evidence-based and model-based approaches provide the insights, information, and tools to help with priority setting and to suit action to the word.
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CHAPTER 10

FINDINGS, DEBATES AND RECOMMENDATIONS

10.1.SUMMARY

Introduction This book describes population health as influenced by its macro- and micro-
determinants. Doing so, it uses the possibilities of a lifetime multi-state modelling approach
to describe health states and changes in health states. The results are descriptions of the
disease process and related health care costs at different aggregation levels in populations.

Results The developed multi-state models allow for analysing dynamic disease processes
throughout a lifetime in relation to the actual stage of the health transition. The dynamic
components are threefold: 1) the substitution, clustering and synergism of health
determinants and diseases, 2) the effectiveness and efficiency of health services, and 3) the
effect of ageing of populations in quantitative and qualitative terms as early and also late
survival improves. At all stages, there is a trade-off with other diseases when a first disease is
treated. The model approach quantifies the effects and allows an analysis in time. Chapter 4
shows that substitution and competition of multiple health risks, at all ages, may partly
explain the lack of results of the introduction of health programmes as in international
health development. It shows also that multiple, also low cost, roads to population health
exist by elimination of health risks and by improvement of disease survival. Computation
of optimal pathways is possible. The chapters on stroke and diabetes show the
relationship of health intervention mixes, available resources, health benefits, and
optimisation options. The stroke analysis shows that, in case of high available budgets,
costly clinical interventions for all patients can be more cost-effective than low cost
clinical interventions for small groups of high-risk patients. The diabetes chapter shows
that, under low available budgets, low cost clinical interventions for small groups of high-
risk patients can be more cost-effective than prevention.

The general finding is that multi-state models allow for computation of multiple, optimum
paths to health throughout a lifetime, depending on the societal resources available.

Model validation More model calibration is necessary and possible. An important free variable
to be used for calibration is the non-attributable incidence of diseases. The population
attributive risk approach should be developed further to account for regression dilution bias
and the occurrence of multiple diseases and multiple determinants. Another calibration
parameter is the effectiveness of prevention and curative services in daily settings. A third
group of calibration parameters is disease-specific mortality and morbidity. Transparent
presentation of models and assumptions promotes expert validation.

Research areas The issues in health are 1) the development of health budget allocation
mechanisms based on intervention effectiveness and efficiency on a lifetime basis, 2) the
assessment of the relative contributions of determinants during a lifetime, especially to
healthy aging, 3) the assessment of the alleged population effects of health interventions.

Conclusion The research quantifies the effects of health determinants on population health,
accounting for uncertainties. It generates information on expected health gains and
medical costs throughout a lifetime of health interventions. It enables policy makers to
choose those options that, given available resources, maximise health.
10.2. MAIN FINDINGS: ROADS TO HEALTH

This chapter gives the findings, controversies and recommendations related to the results of the modelled changes in population health reported in the previous chapters. Last, some specific recommendations are formulated for ongoing research efforts.

The book has described the dynamics of disease occurrence in populations on a lifetime basis. It first gives an overview of the major known health determinants i.e. the health risks and health services that may play a role in determining the transitional changes in population health. Next, it describes the chosen analytic approach in more details and the steps to take, given a research question on changing disease occurrence, disease morbidity, and mortality. The book postulates that a lifetime multi-state modelling approach can be useful to describe disease processes and health care costs in the population and outlines the approach in the second chapter. Next, it studies mortality decline in relation to observed changes in the health determinants in three countries and projects future changes in mortality based on official projections of health determinants. Then, the book reports specific the allocative options of health interventions on a lifetime basis for two example diseases both presenting with morbidity and mortality i.e. stroke and diabetes mellitus.

After describing various case studies in the five application sections, a number of conclusions can be drawn. Multi-state modelling allows for analysing dynamic disease processes throughout a lifetime in relation to the actual stage of the health transition in a country. The dynamic components are threefold: 1. the substitution, clustering and synergism of health determinants and diseases, 2. the effectiveness and efficiency of health services, and 3. the effect of ageing of populations in quantitative and qualitative terms as early and also late survival improves. At all stages, there is a trade-off with other diseases when a first disease is treated. The model approach quantifies these effects and allows for an analysis in time. Chapter 4 shows the substitution and competition of multiple health risks, at all ages, and this will partly explain the lack of results of the introduction of health programmes in international health co-operation.

Increased disease survival

Figure 10.1. One, conceptual presentation of ‘roads to health’ along two selected dimensions. On the diagonal axis the gain in life expectancy (\(e\)) is depicted in time while the x- and y-axis show two dimensions of health improvement i.e. increase in life expectancy.
The conceptual diagram in Figure 10.1 illustrate that for the three countries studied different health determinant clusters may play a role in setting the life expectancy level. The diagram depicts transitional pathways along two axes: an axis of disease survival and one related to protection from health risks i.e. decreasing incidence. On the x-axis the life expectancy gain attributed to increased water supply and sanitation and socio-economic status can be situated and on the y-axis the gain through improved disease survival attributable to food availability, nutritional status and curative health services. Other cluster categories might be possible, however the two chosen have both their typical effect on the occurrence of disease. Decreased incident leads to less disease. Increased survival implies longer periods spent with disease, however maybe of less severity. In the early times improvement came through macro-determinants like nutrition, literacy level and economic development and, if still necessary, through sanitation. In recent times simultaneous improvements in various health determinants may have synergistic effects and can include modern insight in prevention (like immunisation) and treatment (antibiotics). Hence, the results of this same chapter imply that multiple, also low cost, roads to population health exist by elimination of health risks and by improvement of disease survival. Computation of optimal pathways is possible. The chapters on stroke and diabetes show the relationship of health intervention mixes, available resources, health benefits, and optimisation options. The stroke analysis shows that, in case of high available budgets, costly clinical interventions for all patients can be more cost-effective than low cost clinical interventions for small groups of high-risk patients. The diabetes chapter shows that, in case of low available budgets, low-cost clinical interventions for small groups of high-risk patients can be more cost-effective than prevention. The general conclusion is that multi-state models allow for computation of multiple, optimum paths to health throughout a lifetime, depending on the societal resources available.

10.3. THE SCIENTIFIC DEBATE: THE DETERMINANTS OF HEALTH

Controversies in the research on the health determinants complicate the acceptance and the applicability of multi-state model outcomes. They can be grouped in two categories: lack or disagreement of knowledge on the net contribution of each determinant of health (Caldwell, 1991; Cumper, 1986; Rose, 1991; Taubes, 1995) and disagreement among health policy makers on how to improve population health (Niessen et al, 2000). This section sketches deals with the first issues.

Different conceptual approaches to health show disagreements within the determinants of health debate (Frenk, 1993; Ruwaard et al., 1993; Vallin, 1992). The public health uncertainties relate to the estimation of the relative contributions of the determinants to health. This will most likely depend on the transitional stage and they might be substituting or synergetic (Duchene, 1993). The role of ageing process and its influence on the occurrence of morbidity as a health determinant during the last stages is also rather unclear and may depend on the disease studied (Barendregt and Bonneux, 1998).

Social-economic status as broad determinant of disease There is substantial evidence from studies in the Western European countries that higher income, as well as higher social status, is
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correlated with longevity and good health (Townsend, 1990; Cooper, 1990; Marmot and Elliott, 1994; Rowland et al., 1993; Phillips and Verhasselt, 1994). This view states that increased population health follows increased national wealth and development. In other words, individual illness is perceived as an outcome of society's 'ills' (Hurowitz, 1993). Specification of the association between income and health status has led to an increase in the appreciation of other broad health determinants as education, nutrition, water and sanitation. These factors might have their independent contribution in the promotion of health (McKeown, 1972). Present thinking seems to contain a mixture of the former approaches: multi-sector synergism and economic investments (World Bank, 1993; Niessen, 2000). The various determinants can be included within the multi-state modelling approach. The input values for their contribution to disease incidence and survival and mortality depend solely on the presence and quality of empirical research.

Health services as a determinant of health In this view, appropriate use of high quality medical care is seen as contributory to population health. In the eighties more evidence was produced that increased expenditure on medical care is an important intervention to lower mortality and morbidity specially in the later stages of the health transition (Fries, 1981; Pison, 1993; Mackenbach, 1988). In the two decades before this view suffered severe criticism from public health specialists (McKeown, 1976) and in the public domain (Illich, 1974). Within the health sector itself, there is an internal debate: preventive services versus curative services (WHO, 1981; VWS, 1986). Prevention of illness is considered to be less expensive and more effective also in case of chronic diseases (LaPorte, 1993; VWS, 1992). Opponents (Rose, 1992) may state that modern preventive interventions, especially in high-risk groups, can be costly, and less cost-effective, and may cause much unnecessary side effects. Recently, the absolute risk approach has been developed and proven to be more cost-effective than an approach based on single risk thresholds (Niessen en Redekop, 2003; Murray et al. 2002). The studies show that it would be cost-effective to first search for population-based interventions and shifts in the distribution of health risk levels by a number of points to have large impacts. The preceding chapters included so far only the positive effects of (secondary) prevention and cure in the model structure and not the side effects as these are within the culturally determined domains and subject to changes. Therefore, the outcomes of the present research in chapters 6, 7 and 8 confirm only partially Rose's point of view.

Ageing as a health determinant Ageing and its consequences are heavily disputed items within the debate concerning old-age morbidity (Verbrugge, 1989; Olshansky, 1990, 1991). The debate is whether the human life span is inherently limited or whether it can be expanded (Ruwaard, 1993; VWS, 1992). The mortality transition that occurred in this century in most countries includes an increase in life expectancy at birth and in remaining life expectancy also for the higher age groups. Some suppose an upper limit to life expectancy at birth not exceeding some 85 years (Fries, 1980) and a remaining life expectancy of 7 years for men and 9 years for women of 80 years old (Murray, 1994). Others state that human life span can be further manipulated by technology. The average human life span could be as high as 99.2 years (Manton et al., 1991). In our rough computation (chapter 4) this is estimated at 90 years at birth, on average.

The question how the health transition influences the disability experience throughout life remains unanswered in this book. There is a tendency to conclude that it increases with the
Discussion

increase of the life expectancy (Verbrugge, 1984; Crimmins et al., 1989; Olshansky et al., 1991; Barendregt & Bonneux, 1998). The morbidity associated with the fundamental aging process itself might have greater opportunity for expression, but might be less severe as survival improves.

Consequence for the use and structure of the models (1) The uncertainties regarding parameter values are scientific uncertainties. There might be consensus on the modelled structure but not on parameter values related to programme effectiveness. The health effects of health services are modelled through the service-effectiveness functions. In the model, it is assumed that at least part of the historical gains in health is somehow strongly or weakly associated to one or more types of service provision.

The relevance of ageing as a health determinant is twofold: 1) a number of associated health risks in the modes are described as increasing with age, and 2) as the population is aging in later stages of the transition the absolute desired health gain increases and hence the demand for health and health care. The relevant parameters regarding ageing are those that are important at the end of the health transition when the known causes of disease are disappearing. These parameters fall within four categories: 1) the basic, possibly biological, risks of mortality from other causes, 2) the basic risk of becoming incident for one and/or two of the modelled diseases, and 3) the risk of becoming prevalent of another disease not modelled, and 4) the standard risks of becoming disabled due to a particular disease. Model experiments can be done in relation to these four categories of parameters although they are bound to remain explorative. The reduction of e.g. the basic mortality risk to 75% in our model results in a life expectancy of 98 years. More epidemiological research is needed especially among the oldest to collect just the basic disease data to be able to answer questions on the occurrence of disease and death among these groups.

10.4. THE POLICY DEBATE: HOW TO IMPROVE LIFETIME HEALTH?

The policy uncertainties are related to the perceived policy relevance of health as well as the scientific (medical, epidemiological, or health economics) debate on the determinants of health. There are two main related themes: 1) the importance of health services in the society, 2) the type of social or health policy interventions. The issues are parallel to the public health controversies.

Allocation of health resources. This debate focuses on whether and how to provide health services within a collective context. The two domains are how large should the health care package be and the role of the cost-effectiveness approaches (Mooney and Creese, 1993). The debate on coverage of cure and care services can easily be associated with those who stand on the pole of ‘health as a human asset’ in the policy relevance debate and those who stand a ‘human capital’ view. In both approaches, costs and effects considerations play a role. In a ‘human asset’ approach more value for money in the health services makes it possible to extend coverage or treat more patient categories (Abel-Smith, 1972; Lee and Mills, 1983). In this view, the “selective” primary health care programs should be favoured based on cost-effectiveness criteria (Walsh et al., 1993; Grosse, 1980).

Comprehensive or selective health policy. Comprehensive health care permeates many, also non-medical, aspects, of daily life. Initially it centred on the prevention of illness. When health
care is meant to be comprehensive; it includes social elements such as good housing and sanitation, pollution control, road improvements, encouragement of public transport, a safe work environment, stable interpersonal relationships, sufficient income, and education (Hurowitz, 1993; Normand, 1991). Almost all nations at Alma Ata (WHO, 1981) welcomed the broad program of ‘primary health care’ as an operationalisation of comprehensive health care. Selective medical care advocates focus on diagnosing and treating of health risks and diseases usually after they have developed. The notions “selective” primary health care (Walsh et al, 1993) or “essential medical care package” (World Bank, 1993) are commonly used referring to this view.

Consequence for the use and structure of the models (2) Both the variations in the provision of services as well as a number of multi-sector approaches can be included in the modelling approach as possible pathways through the health transition. As health priorities setting usually is attempted at national level, expanded use of multi-state models would require more details in relation to health services provision and the effects on the disease dynamics (see examples in chapter 4 and 5) and the literature (Murray et al., 1994; Barendregt & Bonneux, 1998; Murray et al., 2002). In practice, priority setting through health providers and insurance companies might be more feasible (Niessen et al., 2000). In the latter case, multi-state modelling might still play a supporting role, although the research perspective might have to change.

10.5. RESEARCH RECOMMENDATIONS

The objective of this research is the description and analysis of disease occurrence in various stages of socio-economic development in support of health policy (chapter 1). For this, methods are necessary that can describe changes in population health on a lifetime basis because of changes in health determinants. The development of a generic multi-state population health modelling approach has allowed computing changes in population health as the consequence of changes in health determinants (chapter 2). The modelling approach links changes in the main macro- and micro-determinants with changes in disease incidence and survival, such as environmental and socio-economic changes, nutrition, life style, and health interventions. We have applied the approach to a number of case studies populations (chapter 3) and, in a more detailed way, to specific diseases i.e. stroke and diabetes (chapter 4 and 5). In all chapters, we have reported calibration and validation of the models. Uncertainties remain relating the possibilities of validation of the model at more de-aggregated levels, the model structure (chapter 4 and 5) and the usefulness of results for health policy (chapter 6).

This book observes the start of multi-state modelling of population health in epidemiology, demography, public health, and health economics research. Up to now there are relatively few related research efforts. Recently, there is more attention for the lifetime approach (Aboderin I et al, 2001). The designs, implementation, and application of generic multi-state approaches have been initiated. As summarised in the section on controversies, a number of issues remain to be taken care of to improve the quality of the modelling further. This is elaborated in the next section.
10.5.1. FURTHER MODEL VALIDATION

One of the major issues to address is the validity of the model structure and its results. More model calibration and validation can and should take place. Validation can be structural validation (chapter 3) or external validation, using external time series (chapters 4 and 5). The developed models have relatively few free variables that can be used for calibration and reproduction of population-based time series of morbidity and mortality. An important free variable to be used for calibration is the non-attributable incidence of diseases. In combination with the risk-attributable fraction, it results in the observed disease incidence. The population attributive risk approach should be developed further to account for regression dilution bias and the occurrence of multiple diseases and multiple determinants. Another important calibration parameter is the effectiveness of prevention and curative services in daily settings. Related parameters, such as coverage, are usually based on cross-sectional studies. Incidentally, longitudinal follow-up may be able to give data on day-to-day effectiveness. Also comparison with special population groups that have remained without an intervention may give supportive evidence like studies on religious, cultural groups, on the uninsured, or on 'natural' experiments like war or strikes. A third group of calibration parameters is disease-specific mortality and morbidity. This group can be used for the large disease categories that we used for the applications (chapter 3-5). This would be for Mexico for the period 1950-1990 and for India for the period 1980-1990 based on the Federal Sample Registration Survey. Last, disease-specific calibration is possible for The Netherlands 1900-1990 and also, but with more uncertainties, from 1860 onwards. Expert validation of model structure and assumptions could be more explored and transparency increased. There are good examples of review procedures and panel discussions with researchers, policy makers and the public or its representatives. This also gives more room to account for the more subjective or political choices to be decided upon.

10.5.2. FUTURE RESEARCH

The main characteristic of the multi-state approach is a comprehensive consideration of the quality of life and the cost of disease through a lifetime at the population level. Discussions on these topics cause many heated debates. One can distinguish three groups of important issues in health to be addressed:
1) the development of health budget allocation mechanisms based on proven effectiveness and efficiency of interventions over a lifetime. The basic distributive and priority choices to be made are at the policy and political level. It is here that policy makers can play their important role. They do this by asking the right questions and to state their policy priorities and criteria regarding the involvement of target groups and budgets to be allocated. The involved disciplines, public health, health economics, epidemiology and demography, may all contribute their specific expertise to this important issue.
2) the assessment of the relative contributions of health determinants to lifetime health. The quantitative relationship between the various health determinants, especially socio-economic
status and the health risk factors, is often not clear and changing throughout a life course. It is an area for the epidemiologists and demographers to map out. Important work has been done already. However, in the developed countries there is little information what the determinants are of healthy ageing and how important they are. Also the research of the relationship of genetic information and health is rather limited so far.

3) the assessment of the alleged population effects of prevention and treatment over lifetime (Aboderin I et al, 2001; Ben-Shlomo Y and Kuh D, 2002). There are many confounders and selection biases in the assessment of the effectiveness of preventive or curative health services. Advocates from each area of professional interest (clinical specialists, public health experts, patient groups, health insurance companies, multi-sectoralists, industries, and others) tend to claim a large share in the (potential) declines in mortality and morbidity. Models in health economics and epidemiology can be used to synthesise the information available, define very explicitly the particular health conditions to be improved and to compute health impact and related costs.

10.6. GENERAL CONCLUSION

This book reports the use of the multi-state modelling approach to estimate disease and costs of disease during a lifetime. It is possible to use this method to address general and specific questions on the contribution of the various determinants of population health. Uncertainties can be incorporated in a systematic way in the analyses. The studies on general mortality decline, stroke mortality decline, and the intervention options in stroke and diabetes illustrate the possibilities. They have led to additional understanding of the occurrence of disease and death, of the health effects of health interventions and of the health care costs.

The model outcomes generate information on the expected health gain and medical costs throughout a lifetime of health interventions. It enables policy makers to choose those health options that, given the available resources, maximise population health.
REFERENCES

Summary
SUMMARY OF THE BOOK

Lifetime health
This book describes changing disease occurrence in populations in various stages of socio-economic development, using multi-state lifetime modelling techniques. These techniques analyse population health and health care costs during a lifetime under the influence of changes in health determinants. Two kinds of determinants are distinguished: macro-determinants, such as income status, literacy, availability of food and water, and health services, and micro-determinants, such as smoking, other health risks and specific health interventions.

The first chapter gives a typology of multi-state modelling. It describes how one arrives from a causal qualitative framework at the definition of a multi-state model starting from the research question. Next, it explains how a model can be used to describe, to explain, and to simulate changing disease occurrence in a lifetime. This is in terms of disease incidence, survival, and resulting prevalence, distinguishing single or multiple disease stages. Additional mathematical explanatory models are applied to quantify changes in incidence and disease survival due to changes in health determinants, including those attributable to medical interventions.

A general outline of a comprehensive approach to population health is given, accounting for all its main determinants. This specifies the chosen model approach in terms of point estimates and value distributions for states and flows. It shows how uncertainty in input distributions can account for uncertainties in model results. Results are defined as lifetime health effects and lifetime medical costs, both as intermediate and aggregate outcomes.

Next, the chapter addresses the general research question how to assess changes in population health due to medical interventions and how to optimise the use of resources. These questions may need comparative analyses of important options in prevention and treatment. The questions usually can be grouped into two categories: “How exactly would the intervention influence population health?” and “What are effective and efficient ways to reduce disease and death at the population level?” The first postulate in the chosen approach is that the changes in population health under the influence of health determinants can be described more adequately in a dynamic disease-specific way. The second research postulate is that some “roads to health” may lead to health more quickly and at the expense of fewer resources than other roads. Given the scarcity of resources and the increased demand, there is a need for methods to describe the interactions in a more appropriate way and that can define optimal pathways to maintain and increase present health levels.

Health transitions
The second introductory chapter gives an overview of how most populations of the world during the past century have experienced increases in social welfare and economic development and entered the health transition. These societal changes have shown a concomitant increase in the average life expectancy at birth and a decrease, although slower, in human fertility. The result has been an increase in size and ageing of the world population and a demand for societal resources unprecedented in history. Reduction of health risks and the increased impacts of health services have resulted in a worldwide
Summary

average life expectancy of more than 65 years in spite of an increasing population size. In consequence, all over the world, societies are confronted with a huge demand for health resources due to increased survival and the ageing process. The investments during the later stages of life need to be greater as they show diminishing returns. In contrast, in the poorer regions of the world, population increases have caused a pressing need for continuing investments to just maintain health standards. The awareness has grown that the natural assets relevant to human health, especially food and water, are scarce and diminishing. At the same time, there is more hope. The past decades have shown that, at relatively low budgets per capita, modern insights in prevention and treatment have a lot to offer to the poorer nations.

Generic health modelling

This chapter describes a generic population health modelling approach to address questions on the changes in health determinants and changes in population health. The objective of this approach is to function as a general reference framework when one addresses specific questions related to the influence of health determinants on population health. The main characteristic of such an approach is that it considers all main input-output relationships between population health and both environmental and societal resources. This may include populations living in poverty as well as those living at the highest known income levels. It may be used for analysis of population health in the past and in the future. This approach means a quantitative description of the epidemiology at the population level, taking into account the demonstrated confounding effects of the health determinants, in particular of health risks and health interventions. There are many diseases and many intervention options: there are many ways to fall ill, many causes to die from, and a diversity of instances to actively intervene. There are also many changes in population health that cannot be explained by changes in known determinants of health. Fortunately, there are also many options to prevent people from falling ill, to improve recovery and the quality of survival after falling ill, and to avert premature mortality. Hence, there is no one single way to promote population health best and it will be necessary to adapt the model specifications to a new specific research question and the population under consideration.

The modelling framework can be used to explore, to specify, and to analyse research and policy questions. This is also possible for more specific hypotheses in epidemiology, health economics, demography, and in public health. The approach has been applied in a number of studies: 1) to quantify the contribution of health determinants to mortality decline in India, Mexico and The Netherlands (chapter 4) and 2) to analyse the decline in stroke mortality (chapter 5) and 3) at a more detailed level, to estimate the contribution of health interventions to reduce the disease burden of stroke and diabetes (chapters 6-8).

FIVE STUDIES

Determinants of mortality decline

The importance of the contribution to the mortality decline of improvements in nutritional status, safe water supply, sanitation, income, literacy status, and health services is subject to recurrent debates. The chapter examines how multi-state life table modelling
can synthesise the results from epidemiological studies. It estimates the net effect of each health determinant to changes in differential mortality in India, Mexico and The Netherlands, based on historical scenarios.

The application defines a number of single health states for each of the most important diseases, by age and sex. The model considers all diseases together and also combinations of states. In this way, it allows for competition of health risks i.e. for co-inciding and clustering of determinants as well as of diseases. The competition of risks can be observed especially among both the young and the old. Each population group is defined by a combination of health determinants. The health determinants are clustered into twelve groups while diseases are grouped in 15 categories. Input data on health risks are based on historical figures and official UN scenarios. First, population-attributive risks by health determinant are calculated for each disease based on the selected relative risks from the literature. Next, disease survival is computed based on the disease-specific cure rate and acute and late case-fatality. The input figures for these three parameters are selected from studies on comparable sub-populations. These parameters know a minimum and maximum value each corresponding to a level before and after the transition and are a function of nutritional status and health services level. In this way, the computed results for various health states depend on the changes in health determinants. The calculations reproduce the historical demographical figures of the three countries on population size, crude death rates, crude birth rates and life expectancy at birth. Model outputs have been tested for their validity and consistency. Computed excess total mortality risks by age and sex for all health determinants are similar to those reported in the literature. Calculated annual disease-mortality rates, however, were not always consistent with historical time series.

The results show that improvements in health determinants lead to three distinct effects: 1) the substitution and competition of health risks and diseases causing a certain inertia in the improvement of health 2) the prevention of people becoming ill and, 3) increased survival after entering disease states. There are no unique solutions in the quantification of the role of health determinants in the mortality transition for specified populations. The contribution of each determinant is always depending on the level of other health determinants. Each population is bound to follow its own path in the transition by the country-specific pattern of health determinants.

Time series of historical disease-specific mortality rates should be used for further calibration and validation of model outcomes. This will result in a reduction of uncertainties in parameter values. Historical national data series in a number of European countries will be suitable. More recent time series for Sub-Saharan countries might also be suitable for additional model applications. Many more applications are possible, especially for the design of optimal strategies in the improvement of health determinants.

**Stroke mortality**

Trends in stroke incidence and survival determine changes in stroke morbidity and mortality. This multi-state application examines the extent of the incidence decline and survival improvement in the Netherlands from 1979-1989 and it projects future changes in stroke morbidity over the period 1985-2005 when the country’s population will be ageing. Next, it evaluates the health effects and costs of a number of stroke interventions.
Summary
The multi-state model combines existing literature data and describes stroke epidemiology in the Netherlands. Based on the clinical course of stroke, the model describes historical national age- and gender-specific hospital admission and mortality rates for stroke.
There is evidence of a continuing incidence decline. The most plausible rate of change is an annual decline of -1.9% (range: -1.7; -2.1) for men and -2.4% (range: -2.3; -2.8) for women. Projecting a constant mortality decline, the model shows a 35% decrease of the stroke incidence rate over a period of twenty years. Prevalence rates for major stroke will decline among the younger age groups. However, these will increase among the oldest due to increased survival in the latter. In absolute numbers, this results in an 18% decrease of acute stroke episodes and an 11% increase of major stroke cases. The increase in survival cannot fully explain the observed mortality decline and, therefore, a concomitant incidence decline has to be assumed. Ageing of the population partially outweighs the effect of an incidence decline on the total burden of stroke. Increase in cardiovascular survival leads to a further increase in major stroke prevalence among the oldest.

Stroke care
As illustrated in the first chapter on stroke, in most societies stroke is a major source of morbidity and mortality. There is a big need for effective and efficient ways of prevention and treatment. International consensus is emerging on the contributions of thrombolytic therapy, stroke units, and secondary prevention in improving stroke survival. The study presents the lifetime effects and medical costs of these interventions for the average stroke patient and identifies the optimum intervention mix. We again applied the multi-state model distinguishing states after a first transient ischemic attack, a minor and a major stroke. It includes empirical utility weights for stroke disabilities and 5-year follow-up data on health care utilization and costs. It computes lifetime costs and QALYs lived, by stroke state. We add pooled effectiveness and costs data for the three interventions. The table computes QALYs lived and costs under the seven possible intervention mixes, including uncertainty distributions. A stochastic league table of the mixes presents the results in comparison to the non-intervention baseline.
Baseline results vary by age and sex - up to 2,7-3,7 times for QALYs lived and up to 1,4-2,0 times for cost. Stroke patients may gain a maximum of 0,5 QALYs per lifetime by the three combined interventions. Cost per QALY gained is lowest at younger ages for the stroke units and secondary prevention combined: for men about €55,000 and for women €73,000. Changes in costs and effects are small in comparison to the uncertainty ranges. All intervention mixes that include stroke units will most likely be the optimum choice. The development of acute stroke units deserves priority above medical therapies.

Diabetes morbidity
Diabetes is a major cause of illness and disability in the higher ages groups. Until recently, little attention has been paid to prevention, control, and treatment of complications. In the Netherlands, a program on quality assurance in medical care has started in 1996. Clinical professionals, patient organisations, and health services researchers formulate evidence based guidelines with a concomitant cost-effectiveness analysis. The objective of this effort is to arrive at the provision of effective and efficient treatment packages that reduce diabetes morbidity in the short and long run. As a case study, this application of the multi-state approach is to examine the cost–effectiveness of guideline
recommendations for prevention of nephropathy in diabetes mellitus type 1 and 2. A new multi-state model was developed. Data from international publications on epidemiological surveys and randomised trials, together with national data on health care use and costs, were used to feed the model. A cohort of diabetes patients without renal disease enters the model. The computed outcome measures are complication (end-stage renal disease) free years, QALYs, and life-time medical costs per patient treated according to guideline recommendations or current anti-diabetic strategy. The results show that guideline treatment for type 1 diabetes yields 4.2 complication free life years, at a cost-effectiveness ratio of 13,500 DFL per QALY. Type 2 patients gain 0.2 complication-free life years at a cost-effectiveness ratio of 31,000 DFL per QALY.

Guideline development for diabetes nephropathy, with concomitant multi-state cost-effectiveness calculations, has resulted in a transparent guideline with explicit information on long-term cost and effects. The project also has brought health care providers and health researchers together.

Diabetes care
This chapter presents comparative cost-effectiveness analyses of the Dutch guidelines for intensive control and treatment of complications in type 2 diabetes. It considers two groups of patients: those in primary care and those in secondary care.

A multi-state disease history model describes diabetes and its complications over a lifetime, accounting for uncertainty, and computing medical costs and QALYs and is validated against empirical national figures. Data on the effectiveness and costs of diabetes interventions are from observational current care studies and intensive care experiments. The 16 intervention mixes are compared to a baseline of 10% HbA1c glycemic control. A stochastic league table permits the selection of the optimum intervention mix.

The results show that diabetes interventions may reduce the cumulative incidence of blindness, lower-extremity amputation, and end-stage renal disease by >70% in primary care and >60% in secondary care at a maximum of €20,186 per QALY gained. Primary guidelines add 0.8 QALYs per lifetime. Given low available resources, primary guidelines for complications are most likely the optimum choice.

All current and guideline intervention mixes are cost-effective by Dutch criteria. Current diabetes care is inefficient. If few resources are available, treating complications yields most health benefits. If more resources are available countries may implement all guidelines and improve efficiency.

FINDINGS

Understanding the dynamics of disease occurrence
The book has described the dynamics of disease occurrence in populations and gives an overview of the major known health determinants of mortality decline, health risk factors and health services, and studies the health interventions options in two example diseases i.e. diabetes and stroke. We postulated that a lifetime multi-state modelling approach can be useful to describe disease processes and health care costs in populations and outlined the
approach in the second chapter. After describing various case studies in the five application sections, a number of conclusions can be drawn.

The multi-state models allow for analysing dynamic disease processes throughout a lifetime in relation to the actual stage of the health transition in a country. The dynamic components are threefold: 1) the substitution, clustering and synergism of health determinants and diseases, 2) the effectiveness and efficiency of health services, and 3) the effect of ageing of populations in quantitative and qualitative terms as both early and late survival improves. At all stages, there is a trade-off with other diseases when a first disease is treated. The model approach quantifies these effects and allows for an analysis in time. Chapter 4 shows that substitution and competition of multiple health risks, at all ages, may partly explain the lack of results of the introduction of health programmes as in international co-operation in health. The same chapter shows that multiple, also low cost, roads to population health exist by elimination of health risks and by improvement of disease survival. Computation of optimal pathways is possible. The chapters on stroke and diabetes show the relationship of health intervention mixes options, available resources, health benefits, and optimisation options. The stroke analysis shows that, in case of high available budgets, costly clinical interventions for all patients can be more cost-effective than low cost clinical interventions for small groups of high-risk patients. The diabetes chapter shows that, in case of low available budgets, low cost clinical interventions for small groups of high-risk patients can be more cost-effective than prevention. The general conclusion is that multi-state models allow for computation of multiple, optimum paths to health throughout a lifetime, depending on the societal resources available.

Health policy relevance
As multi-state models allow for quantification of the health and costs influences of each health determinant, including health interventions, they facilitate rational policy making. Broad policy questions in relation to the role of health determinants and health care provision can be specified, modelled and explored like e.g. the use of a zero health expenditure scenarios (chapter 4) and in the use of interventions proposed in guidelines (chapter 5-8). For other broad or detailed policy questions the model approach can be expanded or simplified according depending on the nature of the question. Ethical and political choices will have to remain with the domain of politicians and the public. A lot of the evidence-based approaches, prominent on the national and international agendas for health policy and health research, frequently and increasingly make use of health modelling approaches. It is unclear what the implications of this policy approach are for the production and distribution of health in populations, given the notion of multiple determinants in health. It is equally unclear what kind of barriers there are to the adoption of evidence-based approaches in health care practice. It is unclear what the implications of this policy approach are for the production and distribution of health in populations, given the notion of multiple determinants in health. It is equally unclear what kind of barriers there are to the adoption of evidence-based approaches in health care practice. Chapter 9 outlines the ways in which health policy is informed by the results from health research and health modelling. It summarises approaches in health at three impact levels: inter-sectoral assessment, national health care policy, and evidence-based medicine in everyday practice. Consensus is growing on the role of broad and specific health determinants, including health care, as well as on priority setting based on the burden of diseases. In spite of methodological constraints, there is a demand for inter-sectoral assessments, especially in health sector reform. Initiators of policy changes in other sectors may be held responsible for providing the evidence related to health. There are limited possibilities for priority
setting at the national health care policy level. Hence, there is a decentralisation of responsibilities for resource use towards providers and health insurance companies. They are encouraged to assume agency roles for both patients and society and ask to promote and deliver effective and efficient health care. Governments need to design national frameworks to strengthen their organisation to enhance their roles. The formulation of national health guidelines supported by evidence on effectiveness and efficiency will be one essential element in this process. With the increasing number of advocates for the enhancement of population health in the policy arenas, evidence-based approaches provide the insights, information, and tools to help with priority setting.

RESEARCH RECOMMENDATIONS

Model validation
The book observes the start of multi-state modelling of population health in epidemiology, demography, public health, and health economics research. Up to now there are relatively few related research efforts. The designs, implementation, and application of generic multi-state approaches have been initiated. Important is the validity of the results. More model calibration and validation can and should take place. Validation can be structural validation (chapter 3) or external validation, using external time series (chapters 4 and 5). The developed models have relatively few free variables that can be used for calibration and reproduction of population-based time series of morbidity and mortality. An important free variable to be use for calibration is the non-attributable incidence of diseases. In combination with the risk-attributable fraction, it results in the observed disease incidence. The population attributable risk approach should be developed further to account for regression dilution bias and the occurrence of multiple diseases and multiple determinants. Another important calibration parameter is the effectiveness of prevention and curative services in daily settings. Related parameters, such as coverage, are usually based on cross-sectional studies. Incidentally, longitudinal follow-up may be able to give data on day-to-day effectiveness. Also comparison with special population groups that have remained without an intervention may give supportive evidence like studies on religious, cultural groups, on the uninsured, or on ‘natural’ experiments like war or strikes. A third group of calibration parameters is disease-specific mortality and morbidity. This group can be used for the large disease categories that we used for the applications (chapter 3-5). This would be for Mexico for the period 1950-1990 and for India for the period 1980-1990 based on the Federal Sample Registration Survey. Last, disease-specific calibration is possible for The Netherlands 1900-1990 and also, but with more uncertainties, from 1860 onwards.

Expert validation of model structure and assumptions could be more explored and transparency increased. Examples are review procedures and panel discussions with researchers, policy makers and the public or its representatives. This would also give more room to account for the more subjective or political choices to be a priori made.

Future research
The main characteristic of the multi-state approach is a comprehensive consideration of disease occurrence, disability and the cost of disease through a lifetime at the population
Summary

level. Discussions on these topics cause many heated debates. One can distinguished
three groups of important issues in health to be addressed:
(1) the development of health budget allocation mechanisms based on proven effectiveness
and efficiency of interventions, taking other criteria for priority setting into account. The
basic distributive and priority choices to be made are at the policy and political level. It is
here that policy makers play an important role. They do this by asking the right questions
and to state their policy priorities and criteria regarding the involvement of target groups
and budgets to be allocated. The involved disciplines, public health, health economics,
epidemiology and demography, may contribute all their own particular expertise to this
important issue.
(2) the assessment of the relative contributions of health determinants. The quantitative
relationship between the various health determinants, especially socio-economic status and
the health risk factors, is often not clear and changing. It is an area for the epidemiologists
and demographers to map out. Important work has been done already. However, in the
developed countries there is little information what the determinants are of healthy aging
and how important they are. Also the research of the relationship of genetic information
and health is rather limited so far.
(3) the assessment of the alleged population health effects of prevention and treatment.
There are many confounders and selection biases in the assessment of the effectiveness
of preventive or curative health services. Advocates from each area of professional interest
(clinical specialists, public health experts, patient groups, health insurance companies, multi-
sectoralists, industries, and others) tend to claim a large share in the (potential) declines in
mortality and morbidity. Models in health economics and epidemiology can be used to
synthesise the information available, define very explicitly the particular health conditions to
be improved and to compute health impact and related costs.

GENERAL CONCLUSION

This research reported uses the multi-state modelling approach to estimate disease and
costs of disease during a lifetime. It is possible to use this method to address general an
specific questions on the contribution of the various determinants of population health.
Uncertainties can be incorporated in a systematic way in the analyses. The studies on
general mortality decline, stroke mortality decline, and the interventions options in stroke
and diabetes illustrate the possibilities. They have led to additional understandings of the
occurrence of disease and death, of the health effects of health interventions and of the
health care costs. The approach generates information on expected health gain and
medical cost of health interventions throughout a lifetime. It enables policy makers to
choice those health options that, given the available resources, maximise population
health.
SAMENVATTING

Leven in gezondheid
Dit boek beschrijft de veranderingen tijdens het leven in het voor komen van ziekte en sterfte in de bevolking tijdens verschillende stadia van sociaal-economische ontwikkeling. Er wordt gebruik gemaakt van een rekenmethode die veelsoortige gezondheidsstoestanden kan onderscheiden. De methodiek analyseert ziekte en kosten van ziekte onder de invloed van determinanten van gezondheid tijdens het leven. Twee soorten determinanten worden onderscheiden: determinanten op macroniveau, zoals inkomen, onderwijs, toegang tot voedsel, drinkwater en gezondheidszorg, en determinanten op microniveau, zoals roken en andere gezondheidsrisico’s, en specifieke gezondheidsinterventies.

Het eerste hoofdstuk geeft een typologie van de onderzoeksmethode. Het beschrijft hoe men, afhankelijk van de onderzoeksvraag, vanuit een kwalitatieve omschrijving van het ziekteproces de gezondheidsstoestanden binnen het rekenmodel defnieert. Vervolgens wordt uitgelegd hoe men de methode kan gebruiken om het voor komen van ziekte te beschrijven en te verklaren om te analyseren hoe ziekten tijdens het leven kunnen optreden. Hierbij wordt rekening gehouden met ziek worden, met overleven van ziekte en ook met langdurig ziek blijven, waarbij dan een of meer ziekteetoestanden naar ernst kunnen worden onderscheiden. Om het krijgen en overleven van ziekte te kunnen toetsen aan veranderingen in determinanten van gezondheid, inclusief medische interventies, worden andere additionele verklarende berekeningen toegepast.

Vervolgens wordt een algemene schets gegeven van een integrale benadering van volksgezondheid, waarbij men rekening houdt met alle belangrijke determinanten. Hierin wordt de methodiek van de bijbehorende modelbenadering in detail aangegeven via specificatie van gezondheidsstoestanden en overgangen tussen deze toestanden, uitgedrukt in zowel puntschattingen als in verdelingen van invoerwaardes. Het laat eveneens zien hoe onzekerheden in invoergegevens worden weerspiegeld in onzekerheden van resultaten. De uitkomstgegevens worden uitgedrukt in gezondheidseffecten en medische kosten, zowel in intermediaire als geaggregeerde termen.

Hierna wordt ingegaan op de gestelde onderzoeksvraag naar de kwantificering van gezondheidseffecten van gezondheidsprogramma’s en hoe men de beschikbare middelen optimaal kan aanwenden. Deze vragen impliceren veelal een vergelijkende analyse van opties in preventie en behandeling. De vragen vallen meestal uiteen in twee groepen: “Hoe precies beïnvloedt het desbetreffende programma de volksgezondheid?” en “Wat zijn effectieve en efficiënte manieren om ziekte en sterfte op bevolkingsniveau te reduceren?” Het eerste uitgangspunt hierbij is dat deze effecten van gezondheidsdeterminanten het beste kunnen worden beschreven vanuit een dynamisch, ziekte-specifieke benadering. Het tweede uitgangspunt is dat sommige wegen naar gezondheid sneller naar het doel, een gezond leven, leiden dan andere en met gebruik van minder middelen.

Gegeven de schaarste aan middelen en een wereldwijd snel toenemende vraag naar zorg, is er een behoefte aan methodieken die de samenhang beter beschrijven en die kunnen aangeven wat optimale strategieën zijn om gezondheid te handhaven en te verbeteren.
**Samenvatting**

*Gezondheidstransities*

Het tweede hoofdstuk schetst de toename die de meeste populaties in de wereld de laatste twee eeuwen hebben ervaren in sociaal-economische ontwikkeling en resulterende gezondheidstransitie. De maatschappelijke veranderingen gaan gepaard met een toename van de gemiddelde levensverwachting bij de geboorte en een afname van de vruchtbaarheid. Het gevolg is de wereldbevolking in omvang enorm is toegenomen en ook is verouderd, en dat de vraag naar bestaansmiddelen groter is dan ooit tevoren in de geschiedenis. De afname van gezondheidsrisico’s en de toegenomen effecten van de gezondheidszorg hebben, ondanks de toegenomen omvang van de wereldbevolking, geleid tot een wereldwijde gemiddelde levensverwachting van meer dan 65 jaar. De wereldpopulatie groeit met een gemiddelde van 1.5% per jaar. Op dit moment wordt de omvang van de wereldbevolking in het jaar 2050 geschat op ongeveer 10 miljard. Dit wordt voor ongeveer de helft veroorzaakt door de huidige omvang van de vrouwelijke populatie in de vruchtbare leeftijd. De resterende helft wordt voor een derde bepaald door een geraamde verdere toename in levensverwachting en voor twee derde doordat het vruchtbaarheidsniveau boven vervangingsniveau blijft. Als gevolg worden samenlevingen over de hele wereld geconfronteerd met een enorm toegenomen vraag naar gezondheidszorg. Dit wordt versterkt doordat investeringen op hogere leeftijd groter dienen te zijn omdat er vaak sprake is van een verminderde meerprijs. Als schril contrast veroorzaken de bevolkingstoenames in armere landen van de wereld een nijpende behoefte aan voortdurende investeringen om alleen al het huidige gezondheidsniveau te handhaven. Het besef is gegroeid dat ook natuurlijke hulpmiddelen met invloed op de gezondheid, zoals voedsel en drinkwater, schaars en eindig zijn. Tegelijkertijd is er meer hoop. De afgelopen decennia hebben laten zien dat moderne inzichten in preventie en behandeling, voor een relatief laag budget per hoofd van de bevolking, veel te bieden hebben aan de armere bevolkingsgroepen.

*Een algemene gezondheidsbenadering*

Dit hoofdstuk werkt de algemene schets van de gekozen integrale modelbenadering verder uit om de effecten van gezondheidsdeterminanten nader te kunnen specificeren. De benadering is bedoeld als referentiekader bij de specificatie van onderzoeksvragen. Het karakteristieke van een dergelijke benadering is de beschouwing van alle belangrijke interacties tussen volksgezondheid en beschikbare natuurlijke en maatschappelijke middelen. Het kan zowel gaan om een bevolking die in armoede leeft als een bevolking op het hoogste welvaartsniveau. Het is van nut bij gezondheidsanalyses van historische veranderingen en bij toekomstverkenningen. De benadering betekent een kwantitatieve beschrijving van de epidemiologie zoals deze zich op bevolkingsniveau voordoet, waarbij men rekening houdt met de invloeden van andere determinanten van gezondheid, in het bijzonder risicofactoren en medische interventies. Er bestaan vele ziekten en vele behandelmogelijkheden en er zijn vele oorzaken van ziekten, vele oorzaken van overlijden en een verscheidenheid aan momenten om te handelen. Ook zijn er vele ontwikkelingen in het ziekteproces die men niet aan bekende factoren kan toeschrijven. Er zijn ook vele mogelijkheden om te voorkomen dat mensen ziek worden, om ze te genezen, de kwaliteit van overleven te verbeteren en voortijdige sterfte af te wenden. Er
Samenvatting

bestaat derhalve geen unieke of beste manier om de volksgezondheid te bevorderen en daarom is het telkens weer nodig de onderzoeksmethode aan te passen aan de onderzoeks vraag, aan de populatie die bestudeerd wordt en periode die men wil beschouwen. Zoals in het eerste hoofdstuk is aangegeven kan de benadering worden gebruikt om onderzoeks- en beleidsvragen te exploreren, te specificeren en door te rekenen. Dit is ook mogelijk voor meer specifieke hypotheses binnen de epidemiologie, gezondheids economie, demografie of maatschappelijke gezondheidszorg. De generieke rekenmethode is in een aantal studies toegepast: 1) om de bijdrage te bestuderen van gezondheidsdeterminanten aan sterftedaling in India, Mexico en Nederland, 2) om de daling van sterfte door beroerte in Nederland te analyseren en 3) op een meer gedetailleerd niveau om de bijdrage te omschrijven van interventies tot reductie van ziektenlast van beroerte en diabetes.

VIJF STUDIES

Sterftedaling: wegen naar gezondheid
Het belang van de bijdrage van verbetering in voedingstoestand, drinkwatervoorzieningen, economische status en onderwijs in de sterftedaling is onderwerp van steeds weerkerende debatten. In dit hoofdstuk wordt de modelbenadering aangewend om het effect van ieder van deze determinanten te schatten op de sterftedaling in India, Mexico en Nederland. Deze studie definiert een enkele gezondheidstoestand voor ieder van de belangrijkste ziekten, naar leeftijd en geslacht. Deze ziekten worden in hun samenhang beschouwd en er wordt rekening gehouden met de afrUIL van gezondheidsrisico’s en het verhoogd optreden van combinaties van zowel risico’s als ziekten, op jonge en oude leeftijd. Een bevolkingsgroep wordt gedefinieerd door de combinatie van gezondheidsdeterminanten. Er zijn twaalf clusters van determinanten en vijftien ziektecategorieën. De invoergegevens voor de clusters zijn gebaseerd op historische gegevens. Allereerst wordt berekend wat de bijdrage vanuit de verschillende deelpopulaties is aan de diverse ziekten met de zogenaamde populatie-attributieve fractie. Vervolgens wordt de overleving en het voorkomen van ziekten in deze groepen doorgereken op basis van het genezingspercentage en de acute en late ziekte-spiegelsterfte. Deze drie soorten invoergegevens zijn geselecteerd uit studies van vergelijkbare bevolkingsgroepen. Zij kennen een minimum en maximum dat correspondeert met het niveau van vóór en na de gezondheidstransitie. Dit niveau wordt beïnvloed door de voedingstoestand en het niveau van de gezondheidszorg. De gevonden uitkomsten over het voorkomen van ziekte zijn op deze wijze afhankelijk van verandering in gezondheidsdeterminanten.

De berekeningen reproduceerden zo de historische demografische gegevens van de drie landen, zoals levensverwachting, sterfte, geboorte, en bevolkingsomvang. De berekeningen zijn getest op hun validiteit en consistentie. Zo komt de berekenende leeftijd- en geslachtspecifieke totale sterfte overeen met de empirische gegevens. De berekende jaarlijkse sterfte aan ziekte, echter, is niet altijd in overeenstemming met de bekende historische gegevens.
Samenvatting

De resultaten laten zien dat verbetering van gezondheidsdeterminanten drie teonderscheiden dynamisch effecten hebben. Ten eerste, tonen deze dat bij gezondheidsprogramma's de afruil met andere risico's en ziekten een zekere inertie veroorzaakt in de verbetering van de gezondheid. Ten tweede is er een groot potentieel om ziek worden te voorkómen worden door reductie van de diverse gezondheidsrisico's. Ten slotte is het mogelijk door verbetering van de overleving van ziekte het gezond zijn te bevorderen. Er bestaat geen ‘beste’ oplossing voor verbetering van gezondheidsdeterminanten om sterfte te verminderen en gezondheid te bevorderen. De bijdrage van één determinant is steeds afhankelijk van de aan- of afwezigheid van andere determinanten. In de gezondheidstransitie volgt een bevolking haar eigen weg naar gezondheid, afhankelijk van het eigen patroon van gezondheidsdeterminanten.

Verder bijstellen en testen van de invoergegevens is nodig en kan geschieden op basis van historische tijdreeksen voor ziekte-specifieke sterfte. Dit zal de onzekerheden in de berekeningen verminderen maar niet geheel wegnemen. Verdere toepassingen zijn mogelijk voor andere landen, ook voor de berekening van optimale strategieën in de verbetering van gezondheidsdeterminanten.

Sterfte aan beroerte


Het model combineert de bestaande literatuurgegevens en beschrijft de epidemiologie van beroerte in Nederland. Rekening houdend met het klinisch beloop van beroerte reproduceert het rekenmodel de nationale gegevens omtrent ziekenhuisopnames en sterfte naar leeftijd en geslacht.

Er zijn aanwijzingen voor een continueren van de incidentiedaling. De meest aannemelijke jaarlijkse daling is 1,9% (spreiding: 1,7;2,1) voor mannen en 2.4% (spreiding: 2.3;2.8) voor vrouwen. Uitgaande van een constante sterftedaling laat het model een 35% afname zien van de incidentie van beroerte over de periode van 20 jaar tot aan 2005. Prevalentie van ernstige beroerte zal dalen onder de jongere leeftijdsgroepen. Echter, deze zal toenemen onder de oudste leeftijdsgroepen door toegenomen overleving. In absolute aantallen is het resultaat een 18% afname van gevallen van acute beroerte en een toename van 11% van ernstige beroerte.

De toename in overleving na een beroerte kan de geobserveerde sterftedaling niet volledig verklaren en daarom moet een gelijktijdige incidentiedaling worden verondersteld. Veroudering in de populatie weegt ten dele op tegen het effect van incidentiedaling op de totale ziektelast door beroerte. Toename van de overleving van cardiovasculaire ziekten zal leiden tot een toename van de prevalentie van ernstige beroerte onder de oudste leeftijdsgroepen.

Zorg voor beroerte

Het vorige hoofdstuk rapporteert dat in de meeste samenlevingen beroerte een belangrijke oorzaak is van ziekte, sterfte en zorggebruik. Er is een grote behoefte aan
effectieve en efficiënte methoden voor preventie en behandeling. Er is een toenemende internationale overeenstemming over het nut van trombolytische therapie, ‘stroke units’, en secundaire preventie om de overleving van beroerte te verbeteren. Deze studie presenteert de levenslange effecten en kosten van deze drie interventies voor de gemiddelde beroertepatiënt en identificeert de optimale combinatie van deze interventies.

De modelbenadering onderscheidt drie gezondheidsstoestanden: de toestand na een tijdelijke beroerte, na een lichte beroerte en na een zware beroerte. De gegevens voor elke toestand worden verrekend met een empirische utiliteitswaarde. Ook worden deze gegevens verrekend met gegevens omtrent het zorggebruik en de kosten, gebaseerd op een studie waarin beroertepatiënten voor vijf jaar werden gevolgd. Het model berekent dan verder de resterende levensduur, de gerelateerde kosten en het aantal geleefde, kwaliteit-gewogen levensjaren (QALYs) voor iedere vastgestelde toestand na beroerte. Vervolgens zijn de effectiviteits- en kostengegevens toegevoegd voor de drie interventies.

De resultaten in geval van niet-behandelen variëren tussen de laagste en hoogste leeftijdsgroep met een factor 2,7-3,7 voor het aantal nog geleefde QALYs en een factor 1,4-2,0 maal voor de levenslange kosten. De gemiddelde beroertepatiënten kunnen maximaal 0,5 QALY winnen door toepassing van de drie interventies. De kosten per gewonnen QALY zijn het laagst op jonge leeftijd voor de combinatie van ‘stroke units’ en secundaire preventie: voor mannen is dit ongeveer €55.000 en voor vrouwen €73.000.

Ziekte door diabetes mellitus
Diabetes mellitus is een belangrijke oorzaak van ziekte en handicap op hogere leeftijd. Tot voor kort is er weinig aandacht geweest voor preventie, controle en behandeling van complicaties zoals nierfalen, blindheid en beenamputaties. In Nederland is in 1996 een programma “Kwaliteitsbewaking in de gezondheidszorg” van start gegaan. Clinici, patientenorganisaties en gezondheidsonderzoekers hebben gezamenlijk richtlijnen geformuleerd op basis van wetenschappelijke bewijslast en kosteneffectiviteitgegevens. Het doel is om te komen tot een effectief en efficiënt zorgpakket dat de ziekte door diabetes reduceert op de korte en lange termijn. Als voorbeeld onderzoekt deze studie de kosteneffectiviteit van de richtlijnen voor de preventie van nefropathie in diabetes mellitus, type 1 en type 2.
Samenvatting

Ook hier maakt het model gebruik van gegevens uit internationale epidemiologische publicaties en van gerandomiseerd onderzoek. Deze worden gecombineerd met nationale gegevens over zorggebruik en kosten. Het model rekent de gegevens door voor een groep van diabetespatiënten die aanvankelijk zonder complicaties zijn. De uitkomstmaten zijn jaren zonder complicaties (= zonder terminaal nierlijden), QALY's, en de medische kosten per behandelde patiënt gedurende het resterende leven. De bestudeerde behandeling bestaat óf uit de bestaande zorg óf uit zorg volgens richtlijnen.

Het resultaat laat zien dat behandeling volgens richtlijnen bij type 1 patiënten tot 4,2. complicatievrije jaren leidt, bij een kosteneffectiviteitratio van 13,500 DFL per gewonnen QALY. Type 2 diabetes patiënten winnen 0,2 complicatievrije jaren bij een kosteneffectiviteitratio van 31 000 DFL per gewonnen QALY.

Richtlijnontwikkeling voor diabetes nefropathie met een gelijktijdige kosteneffectiviteitsanalyse heeft geresulteerd in een transparante richtlijn met expliciete informatie over de kosten en effecten op de lange termijn. Daarnaast heeft de studie zorgverleners en gezondheidsonderzoekers samengebracht.

Zorg voor diabetes

Het hoofdstuk presenteert de vergelijkende kosteneffectiviteitsanalyses van de Nederlandse richtlijn voor intensieve controle en behandeling van complicaties van diabetes type 2. Het beschouwt twee groepen van patiënten in Nederland: de groep behandeld in de eerstelijnszorg en de groep in de tweedelijnszorg. Het toegepast ziektemodel voor diabetes is probabilistisch en onderscheidt verschillende gezondheidstoestanden. Het berekent het optreden van de complicaties gedurende het resterende leven en vervolgens de gerelateerde totale medische kosten en QALY's. Het model is gevalideerd met nationale empirische gegevens. De gegevens over effectiviteit en kosten van behandelingen van diabetes zijn van observationele studies en experimenten met intensieve behandeling. Zestien behandelingsopties zijn vergeleken met de situatie van zeer slechte controle: een instellingsniveau van 10% HbA1c. Tot slot worden in een stochastische tabel de optimale behandelingsopties weergegeven.

De resultaten laten zien dat behandeling van diabetes de cumulatieve kans op blindheid, beenamputatie en nierfalen met > 70% in de eerstelijnszorg en > 60% in de tweedelijnszorg kan reduceren, bij een maximum van €20,186 per gewonnen QALY. De richtlijnen in de eerstelijnszorg leiden tot 0,8 QALY's langer leven. De huidige zorg voor complicaties is, als pakket, inefficiënt. In geval van schaarste aan middelen leiden de behandelingen van complicaties het meeste tot gezondheidswinst. Is er geen gebrek aan middelen dan zijn alle richtlijnen de moeite waard om te verwezenlijken en zal dit de efficiëntie bevorderen.

BEVINDINGEN

Inzicht in de dynamiek van ziekten

Het onderzoek beschrijft de dynamiek van het optreden van ziekten in een bevolking en schetst de bijdrage van de belangrijkste determinanten van gezondheid namelijk gezondheidsrisico's en gezondheidszorg. Het rapporteert de behandelingsopties voor twee
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belangrijke ziekten: beroerte en diabetes mellitus. Het uitgangspunt is geweest dat de gekozen demografische modelbenadering beter dan tot nu toe in staat is ziekteprocessen en gerelateerde medische kosten in beeld te brengen, en benut kan worden om optimale keuzes vast te stellen. Nu de methodiek en de vijf studies zijn beschreven kunnen er een aantal algemene gevolgtrekkingen worden gemaakt.

Het onderscheid van diverse gezondheidsstoestanden in de modellen maakt het mogelijk de ziekteprocessen tijdens het leven zeer goed te beschrijven, en het niveau van de gezondheidsdeterminanten goed weer te geven i.e. de fase van de gezondheidstransitie in een land te kwantificeren. In alle ontwikkelingsstadia is er een uitruil met andere ziekten wanneer een eerste ziekte is behandeld. De modelbenadering kwantificeert dit effect in de tijd. De dynamisch componenten zijn drievoudig: 1) substitutie, clustering, en synergisme van gezondheidsdeterminanten en ziekten leiden tot inertie, 2) de effectiviteit en efficiëntie van gezondheidszorg leiden aanvankelijk tot afname van ziekte maar, op latere leeftijd, weer tot toename van ziekte, en 3) de uiteindelijke balans van kwalitatieve en kwantitatieve effecten van toenemende overleving van ziekte bepaalt uiteindelijk of afnemende sterfte tot meer of minder ziekte leidt.

Hoofdstuk 4 laat zien dat vervangende gezondheidsrisico’s en ziekten op vooral jonge leeftijd verklaren waarom de slechte gezondheidsstoestand van de bevolking in ontwikkelingslanden zo traag verandert ondanks vele gezondheidsprogramma’s. Hetzelfde hoofdstuk illustreert dat vele, ook relatief goedkope, wegen tot verbetering van de gezondheid kunnen leiden, in het bijzonder door het terugdringen van gezondheidsrisico’s en het verbeteren van de overleving van ziekten. De berekening van optimale keuzes is hierbij mogelijk. De hoofdstukken over beroerte en diabetes tonen de interactie tussen behandelingsopties, beschikbare middelen, mogelijke gezondheidswinst en optimale allocatie. De analyse voor beroerte toont aan dat in geval van ruime beschikbare middelen, kostbare klinische zorg voor alle patienten kosteneffectiever is en tot meer gezondheid leidt dan minder dure secundaire preventie in risicogroepen. Het hoofdstuk over diabetes geeft weer dat in geval van beperkte middelen, minder kostbare, effectieve klinische behandeling in kleine risicogroepen kosteneffectiever zou kunnen zijn dan kostbare preventieve interventies.

De diverse studies tonen aan dat de onderzoeksmethode het mogelijk maakt de optimale mogelijkheden tot gezond leven te kwantificeren, afhankelijk van de beschikbare middelen binnen de gezondheidszorg.

Relevante voor het beleid

Het soort uitkomsten van deze onderzoeksmethodiek kan bijdragen aan de totstandkoming van een rationeel gezondheidsbeleid. Brede beleidsvragen omtrent de rol van gezondheidsdeterminanten en gezondheidszorg dienen te worden vertaald in een modelstructuur, zoals de diverse scenario’s voor macroadeterminanten (hoofdstuk 4), Ook kunnen de introductie van medische behandelingen worden doorgerekend bijvoorbeeld zoals die zijn voorgesteld in de Nederlandse richtlijnen (hoofdstuk 5-8). Ter beantwoording van andere brede of meer gedetailleerde beleidsvragen kan de benadering worden uitgebreid of gesimplificeerd, afhankelijk van de vraag. Ethische en politieke keuzes dienen vanzelfsprekend in het publieke domein te worden behandeld. Veel van het huidige gezondheidsbeleid berust op wetenschappelijke bewijslast en staat prominent op nationale en internationale beleids- en onderzoeksagenda’s en maakt vaak en in
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toenemende mate gebruik van gezondheidsmodellen. Het is onduidelijk wat de gevolgen van een dergelijk beleid zijn voor de bevordering en verdeling van gezondheid in populaties, gegeven het feit dat gezondheid door vele determinanten wordt bepaald. Het is net zo onduidelijk wat de obstakels zijn voor de aanvaarding van wetenschappelijk bewijs in de dagelijkse praktijk. Hoofdstuk 9 schetst de wijze waarop beleidsmakers worden geïnformeerd door dit type gezondheidsonderzoek. Het geeft een samenvatting van de benadering op drie niveaus: intersectoraal onderzoek, nationaal gezondheidszorgbeleid en zorgverlening in de dagelijkse praktijk. Er groeit overeenstemming over de bijdrage van macro- en microdeterminanten, inclusief gezondheidszorg aan de volksgezondheid. Ook is er overeenstemming over prioriteitenstelling op basis van gegevens omtrent ziektebelast. Ondanks methodologische bezwaren is er vraag naar intersectorale evaluaties, vooral op het terrein van sectorale hervormingen. Beleidsmakers in andere sectoren worden wellicht verantwoordelijk gesteld voor informatie betreffende de gevolgen voor de volksgezondheid. Er zijn beperkte mogelijkheden voor prioriteitenstelling op nationaal beleidsniveau. Er vindt daarom een decentralisatie van verantwoordelijkheden plaats voor het aanwenden van middelen naar zorgverlenende instanties en verzekeraars. Deze beide groepen worden aangemoedigd zowel patiënten als maatschappij te vertegenwoordigen en effectieve en efficiënte zorg te leveren en te bevorderen. Regeringen zullen een nationaal kader moeten ontwikkelen om de organisatie van deze groepen te verbeteren en hun rollen te versterken. De formulering van nationale medische richtlijnen is belangrijk in dit proces. Met de toename van diversiteit van actoren bij de beleidsvorming, bieden de benaderingen gestoeld op wetenschappelijke bewijslast, inclusief modelberekeningen, meer inzicht, meer informatie en meer methoden om te komen tot prioriteitenstelling in de zorg.

AANBEVELINGEN

Toetsing van modellen

Dit boek constateert de start van een demografisch modelbenadering in het volksgezondheidsonderzoek zowel binnen de epidemiologie, maatschappelijke gezondheidseconomie, en ook gezondheidszorg, en ook gezondheidszorg. Tot nu toe is er relatief weinig vergelijkbaar onderzoek verricht. Dit boek draagt bij aan het verdere ontwerp, de implementatie en de toepassing van modellen die veelzijdige gezondheidstoestanden onderscheiden. Een belangrijk onderwerp is de verdere ontwikkeling en standaardisatie van methoden van validatie. Calibratie en valideren van modelresultaten blijft steeds noodzakelijk. Dit kan structurele validatie zijn (hoofdstuk 3) of externe validatie op basis van externe gegevens (hoofdstuk 4,5,7 en 8). De ontwikkelde modellen beschikken over slechts een zeer beperkt aantal zogenaamde ‘vrije’ variabelen die kunnen worden benut voor calibratie en de reproductie van tijdreeksen van ziekte en sterftegegevens. Een belangrijke vrije variabele is de non-attributieve incidentie van ziekte. In combinatie met de risico-attributieve fractie, levert dit de observeerde incidentie op. De populatie-attributieve risico-methode dient hiertoe verder te worden ontwikkeld om rekening te kunnen houden met verdunningseffecten en het vóórkomen van multiple risico’s en ook ziekten. Een andere
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belangrijke kalibratie parameter is de effectiviteit van preventie en behandeling in de dagelijkse praktijk. Een belangrijke gerelateerde parameter is de dekkingsgraad van behandeling. Een derde groep relevante parameters is de tijdreeksen van het optreden van ziekte en ziekte-specifieke sterfte (hoofdstukken 3-5, 8). Het zou interessant zijn deze voor Mexico voor de periode van 1950-1990 en voor India voor de periode van 1980-1998 (uit het Federal Sample Registration Survey) nader te kunnen onderzoeken. Tot slot zou het interessant zijn de historische ziekte-specifieke ontwikkeling van sterfte in Nederland zelf nader te onderzoeken voor de periode 1900-1990, of, met meer onzekerheden, vanaf 1860. Expert validatie van de modelstructuur en de aannames dient meer te worden gesystematiseerd en ook de transparantie van dit proces dient te worden uitgebreid. Er bestaan enige voorbeelden van audit procedures en panel discussies van onderzoekers, beleidsmakers en publieke vertegenwoordigers. Dit schept eveneens meer ruimte voor meer subjectieve en impliciete keuzes die tijdens het ontwikkelingsproces gemaakt worden.

Onderzoeksterreinen

De belangrijkste eigenschap van de gevolgde methodiek is een integrale beschouwing het optreden van ziekten, beperkingen, sterfte en kosten van ziekte tijdens een mensenleven. Discussies op dit terrein leiden tot veel debat. Hierin kan men drie hoofdonderwerpenonderscheiden:

(1) de ontwikkeling van methodieken die sectorbrede budgetallocatie studies mogelijk maken, op basis van bewezen effectiviteit en efficiency van behandelingen. De primaire verdelings- en prioriteringsvraagstukken dienen allereerst op politiek beleidsniveau te worden opgelost. Hier is het dat beleidsmakers een belangrijke rol kunnen spelen. Dit kunnen zij doen door de juiste vragen te stellen en hun voorkeuren en criteria voor allocatie van middelen uit te spreken. De betrokken onderzoeksgebieden, gezondheids- en maatschappelijke gezondheidszorg, zullen hieraan ieder hun eigen bijdragen leveren.

(2) de kwantificering van relatieve bijdragen van gezondheidselementen aan de gezondheid. De relaties tussen de verschillende determinanten, zoals sociaal-economische status en gezondheidsrisico’s, is vaak niet duidelijk en aan verandering onderhevig. Dit is een onderzoeksterrein voor epidemiologen en demografen. Belangrijk werk is reeds gedaan. In de ontwikkelde landen is er weinig informatie over de aard en invloed van de determinanten van gezond ouder worden. Ook het onderzoek van de relatie tussen gezondheid en genetische informatie is beperkt tot nu toe. Hier liggen een groot aantal modelmatige en andere methodologische uitdagingen.

(3) de kwantificering van de veronderstelde volksgezondheidseffecten van preventieve en curatieve behandelingen. Op dit terrein zijn er vele verstorende factoren en ook vertekeningen door selectie. Vertegenwoordigers uit de diverse sectoren met name artsen, patientenorganisaties, verzekeraars, onderzoekers van volksgezondheid en klinische zorg, intersectorale onderzoekers, medische industriëen, en andere actoren, hebben de neiging een grote bijdrage te claimen in de (mogelijke) daling van ziekte en sterfte. Modelberekeningen vanuit de gezondheids- en epidemiologie kunnen hierbij gebruikt worden om tot een synthese te komen van de beschikbare informatie. Hierbij is een nauwkeurige definitie van de te beschouwen gezondheidscondities van groot belang. Pas dan kan men overgaan tot een berekening van het potentiële effect op de volksgezondheid en de gerelateerde maatschappelijke (medische en niet-medische) kosten.
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ALGEMENE CONCLUSIE

Het onderzoek gebruikt de modelbenadering om ziekte en kosten van ziekte tijdens het leven beter te kunnen beschrijven. Het blijkt mogelijk met deze methodiek algemene en gerichte vragen te beantwoorden omtrent de bijdrage van de diverse determinanten aan de volksgezondheid. De onzekerheden die hierbij zijn kunnen op systematische wijze worden betrokken in de analyses. De studies van de algemene sterfstedaling, de sterfstedaling bij beroerte, en de behandelingsopties bij beroerte en diabetes illustreren de mogelijkheden. De analyses hebben geleid tot meer inzicht in het optreden van ziekten en sterfte, in de effecten van behandeling en in de ontwikkeling van medische kosten tijdens een mensenleven. De onderzoeksresultaten leiden tot meer informatie over de te verwachten gezondheidsverbetering en kosten van interventies tijdens het leven. Dit maakt het voor beleidsmakers mogelijk die beleidsopties te kiezen die, gegeven de beschikbare middelen, de gezondheid maximaal bevorderen.
RELATED PUBLICATIONS AND MANUSCRIPTS

Chapters 1-3. Lifetime health

Chapter 4. Determinants of mortality decline

Chapters 5 and 6. Stroke and stroke care


Chapters 7 and 8. Diabetes and diabetes care


Chapters 9 and 10. Health policy


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His previous work, at the National Institute for Public Health (RIVM), included the design of a model for the Dutch health system (1996). Before that, he worked at this institute for 3 years on modelling human reproduction and health, in co-operation with the Groningen Population Research Centre. Spin-offs were studies on India, Mexico, and The Netherlands for the 1st Global Environmental Outlook by the UN Environmental Programme (UNEP). Before that, he had started health modelling at the Erasmus Institute of Public Health.

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