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
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, 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.
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 demographic 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
Summary

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. 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 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 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