PART I

INTRODUCTION
Chapter 1
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.
Chapter 1
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-Schepers; 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:
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
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
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.

![Causal Framework Diagram](https://example.com/causal-framework.png)

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 bio-physiological 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.

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 of a multi-state modelling framework for population health](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
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 $m^a_t$:

$$p^a_t = p^a_{t-1} + i^a_{t-1} \left(1 - p^a_{t-1}\right) \frac{1}{1 - M^a_{t-1}}$$

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 $t > 0$:  

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\[ M_t^a = 1 - \exp \left( - \left( M_{other}^a + \sum_d M_{d,t}^a \right) \right) \]

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>Ischemic heart disease</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>Lung cancer</td>
</tr>
<tr>
<td></td>
<td>All other cancers</td>
</tr>
<tr>
<td>Stroke</td>
<td>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/transition 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):

\[
PAR_R = \frac{P_R \cdot (m_1 - m_0)}{1 + P_1 \cdot (m_1 - m_0)}
\]

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 $P_1$ is the fraction with the risk. When we introduce relative risks, we can rewrite the formula (see also Figure 1.2):

\[
PAR_R = \frac{P_R \cdot (RR_R - 1)}{1 + P_1 \cdot (RR_R - 1)}
\]
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 \( \text{RRs} > 1 \):

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

(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:

\[ \text{PAR}_R = \left\{ P_{R_0} \times (m_{R_0} - m_{00}) + P_{RS} \times (m_{RS} - m_{S}) \right\} / \sum_{ij} P_{ij} \times (m_{ij}) \]  

(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:

\[
PAR_R = \frac{P_R \cdot (RR_R(S) - 1)}{P_{00} + RR_R(S) \cdot P_{R0} + RR_r(R) \cdot P_{RS}}
\]

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 \( PAR_{RS} = PAR_R + PAR_S - PAR_R \cdot PAR_S \). This is possible in the case of multiplicative risks \((RR_{rs} = RR_{r0} \cdot RR_{0s})\) and independently distributed risk factors \((P_{rs} = P_r \cdot P_s)\). 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:

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

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:

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

with:

\[
PAR_R = \frac{P_R \cdot (RR_R(S) - 1)}{1 + P_R \cdot (RR_R(S) - 1)}
\]

\( C \) 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

![Example PAR distribution for blood pressure in relation to stroke incidence.](image)

Figure 1.5. Example of a PAR distribution for blood pressure in relation to stroke incidence. A population distribution of blood pressure and each corresponding relative risk for stroke are used (Niessen and Redekop, 2003).
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)

General public; patients at risk (Niessen et al, 2002; chapter 6).

**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
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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%.

![Figure 1.8](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):

\[
DALE_t^a = \frac{\sum_{i=1}^{100} L_i^t (1 - W_i^t)}{L_i^t} \tag{10}
\]

Here \(L_i^t\) is the number of years lived by the average person of age \(a\) between time \(t\) and \(t+1\). \(W_i^t\) is the average disability weight by age and time, and \(L_i^t\) 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; García-Rodríguez and Cayolli 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
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Figure 1.9. Health expectancy and risk-attributable loss of health expectancy years in time (UNEP, 1997; chapter 4).

...figures, one can compute the weighted life years lived by the population and the weighted life years lost attributed to health determinants. These two figures allow for the calculation of the more general outcome measures as life expectancies, disability-adjusted life years and the DALE or health expectancy. In the figure the DALE-years that are lost, are combined in three categories: those related to 1) a combination of the food and safe water shortages, vector-born diseases and poverty, those related to 2) poverty only and those related to 3) high-income related lifestyle risks such as smoking and hypertension.

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 45-64 65-74 75+</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.20/0.25 0.10/0.11 0.13/0.13</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>0.12/0.03 0.13/0.06 0.17/0.07</td>
</tr>
<tr>
<td>Eye disease</td>
<td>0.11/0.14 0.05/0.05 0.07/0.06</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>0.11/0.11 0.16/0.13 0.20/0.16</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.24/0.22 0.12/0.11 0.15/0.13</td>
</tr>
<tr>
<td>Cellulitis of leg or foot</td>
<td>0.02/0.02 0.02/0.02 0.02/0.02</td>
</tr>
<tr>
<td>Chronic ulcers</td>
<td>0.19/0.24 0.14/0.09 0.18/0.11</td>
</tr>
</tbody>
</table>

Table 1.2. Population-attributive fraction for the costs of diabetes complications, by age, sex, and diabetes-related disease based on prevalence figures and relative risks for the related diseases. (Ossen 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. 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).](image-url)
**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](image_url)

---

*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.
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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.
REFERENCES

15. Edwards RT (2001): Paradigms and research programmes: is it time to move from health care economics to health economics, Health Econ, 10 (7) 635-49.


89. VWS (Ministry of Welfare, Health and Cultural Affairs) (1992): Memorandum Chronic Disease, Rijswijk, the Netherlands.
94. Walter SD (1976): The estimation and interpretation of attributable risk in health research; Biometrics 32 829-49.