Summary and Keywords

In most countries, non-communicable diseases have taken over infectious diseases as the most important causes of death. Many non-communicable diseases that were previously lethal diseases have become chronic, and this has changed the healthcare landscape in terms of treatment and prevention options. Currently, a large part of healthcare spending is targeted at curing and caring for the elderly, who have multiple chronic diseases. In this context prevention plays an important role as there are many risk factors amenable to prevention policies that are related to multiple chronic diseases.

This article discusses the use of simulation modeling to better understand the relations between chronic diseases and their risk factors with the aim to inform health policy. Simulation modeling sheds light on important policy questions related to population aging and priority setting. The focus is on the modeling of multiple chronic diseases in the general population and how to consistently model the relations between chronic diseases and their risk factors by combining various data sources. Methodological issues in chronic disease modeling and how these relate to the availability of data are discussed. Here, a distinction is made between (a) issues related to the construction of the epidemiological simulation model and (b) issues related to linking outcomes of the epidemiological simulation model to economic relevant outcomes such as quality of life, healthcare spending and labor market participation. Based on this distinction, several simulation models are discussed that link risk factors to multiple chronic diseases in order to explore how these issues are handled in practice. Recommendations for future research are provided.

Keywords: chronic diseases, simulation modeling, prevention, aging, comorbidity, health economics

Introduction

Life expectancy has been increasing in most Western countries since the 19th century, due to improved living standards (e.g., better hygiene and food) as well as medical care (Cutler, Deaton, & Lleras-Muney, 2006). These increases in life expectancy combined with the aging of the baby boom cohorts have resulted in an increase in the proportion of elderly people in many Western countries over the past few decades (Christensen, Dobl-
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The increase in the number of the elderly has not yet reached its peak, and the share of those over the age of 65 is expected to grow further (Organisation for Economic Co-operation and Development, 2014). Simultaneously, the growth in healthcare expenditures (HCE) has outpaced growth in gross domestic product (GDP). Since the 1950s, causes of death have changed from mainly infectious diseases to chronic diseases, and medical care has changed in response to this epidemiological transition (Omran, 2005). Many noncommunicable diseases that were previously lethal diseases have become chronic, and this has changed the healthcare landscape in terms of treatment and prevention options (Bech, Christiansen, Khoman, Lauridsen, & Weale, 2011; de Meijer, Koopmanschap, Uva, & van Doornslae, 2011; Koopmanschap, de Meijer, Wouterse, & Polder, 2010; Meara, White, & Cutler, 2004). Much of healthcare spending is currently targeted at the elderly, which has raised concerns regarding the consequences of further aging on HCE. This has raised further concerns about the sustainability of healthcare systems, which are based on the solidarity between different generations (Parr, Li, & Tickle, 2016). Furthermore, as the proportion of GDP that is spent on HCE is increasing, there have been worries about the rate of return of additional investments in medical care (Chandra & Skinner, 2012).

In the context of increasing longevity and increases in healthcare spending, prevention plays an important role as there are many risk factors amenable to prevention policies that cause a high burden of disease (Danaei et al., 2009; Danaei et al., 2010; Lim et al., 2012). For instance, more than 30% of the worldwide burden of disease caused by ischaemic heart disease can be attributed to smoking (Lim et al., 2012). For diseases like lung cancer and chronic obstructive pulmonary disease (COPD), an even bigger part of their burden can be attributed to smoking. More generally, for many important chronic diseases (e.g., diabetes, various types of cancer and heart and lung disease), there are known modifiable risk factors (e.g., smoking, obesity, high blood pressure). Under the heading of the compression of morbidity hypothesis, it has been put forward that preventing disease or disease progression and complications might decrease disease-related costs, thereby countering growing healthcare costs from aging. Indeed, preventing a disease would avoid costs aimed at that particular disease and therefore could lead to decreased healthcare costs in the short run. However, prevention of many diseases will increase longevity. Then, ceteris paribus, people will consume more healthcare in the additional years especially if these additional years are spent in poor health. To what extent the additional healthcare costs in “added” life years outweigh savings in “normal” years differs per disease and type of preventive intervention (Barendregt, Bonneux, & van der Maas, 1997; Bonneux, Barendregt, Nusselder, & Van der Maas, 1998; Grootjans-van Kampen, Engelfriet, & van Baal, 2014; van Baal et al., 2008). Diseases associated with a high mortality risk have a strong negative impact on longevity, especially if these diseases have an early age of onset. The situation is different with chronic or disabling diseases. Persons with such diseases can often live close to the average life expectancy. Nevertheless, chronic diseases may cause a reduction in quality of life and bring about continuous need for healthcare service. However, there may be changes in these mechanisms over time (Grootjans-van Kampen et al., 2014). For instance, the availability of more effective
treatments for circulatory diseases has resulted in increased survival but also higher costs. Consequently, preventing circulatory diseases will result in fewer health gains but in more costs savings. To complicate matters further, many people have multiple diseases, and many diseases are targeted by multiple interventions. As with healthcare spending, it has been suggested that preventing chronic disease might increase labor market participation at older age (Ageing Working Group, 2012; Maestas & Zissimopoulos, 2010; van den Berg, Elders, & Burdorf, 2010; Wubulihasimu, Brouwer, & van Baal, 2015). However, here again it must be taken into account that although prevention may result in production gains by preventing illness, some of the life years that are gained are spent after retirement. Generally, after retirement people consume (both medical and nonmedical goods and services) more than they produce (Meltzer, 1997).

The issues discussed in the previous paragraph illustrate that prevention policies often have an impact on multiple diseases in the long run. This article discusses the use of simulation modeling to better understand the relations between chronic diseases and their risk factors, with the aim to inform health policy. Simulation modeling has an important role in estimating cost-effectiveness (Briggs, Claxton, & Sculpher, 2006; Buxton et al., 1997). Mostly such work aims to evaluate a specific treatment decision for a specific patient group. This requires modeling the consequences of the treatment on the progression of the disease targeted by the treatment. In this type of model, the modeling of disease can be restricted to only the aspects influenced by the treatment. This article, however, focuses on a broader class of models, that are not limited to a specific treatment for a specific disease but that describe how multiple diseases evolve in the general population. Such models might shed light on important policy questions related to population aging and priority setting and are necessary for estimating the effects of prevention, to support foresight study for future health and social security, and to support general decisions and priority setting in public health policy. Such models need to model more than the effects of a single intervention on a single disease and need to contain a broad range of diseases. The article focuses on the modeling of multiple chronic diseases in the general population and how to consistently model the relations between chronic diseases and their risk factors by combining various data sources. It starts by describing the methodological issues in chronic disease modeling and how these relate to the availability of data. Here, there is a distinction between conceptual issues and computational issues and how multiple disease models can be linked to economically relevant outcome measures such as quality of life, healthcare, and labor market participation. The article then discusses the use of chronic disease modeling in health economics and describes how the aforementioned issues are addressed. It concludes with some recommendations for future research.
Methodological Issues in Multidisease Modeling

Simulation modeling of multiple chronic diseases is used in health economics in order to predict future healthcare needs or consequences of time trends in risk factors or to estimate the benefits and costs of interventions aimed at risk factors that influence more than a single disease. For instance, smoking increases the incidence not only of lung cancer but also of ischaemic heart disease, oral cavity cancer, and many more. For broader goals such as priority setting and forecasting studies, this type of model is further expanded with models that include multiple risk factors. In the case of forecasting studies, it is also important that demographic developments relating to differences in size of birth cohorts are included. This section discusses methodological issues that are specifically related to the modeling of multiple diseases and how they relate to risk factors. Here, there is a distinction between conceptual issues and computational issues.

Conceptual Issues

As a starting point for discussing conceptual issues related to the modeling of multiple chronic diseases, see Figure 1. It displays an example causal diagram of how risk factors and chronic diseases may influence economic relevant outcomes such as mortality, quality of life, healthcare use, and labor market participation. Figure 1 displays the causal relationships between body mass index (BMI), diabetes, acute myocardial infarction (AMI), stroke (CVA) and chronic heart failure (CHF). Figure 1 illustrates nicely the complexities in multidisease modeling. For instance, a higher BMI may influence economic outcomes through an increased risk of diabetes which in turn elevates the risk of AMI, CVA, and CHF. In addition, there is a direct effect of BMI on final outcomes that can be interpreted as an indirect effect running through other diseases, illnesses, or impairments not included in the model.

![Figure 1: Example causal diagram describing the relations between a risk factors, multiple chronic diseases and economic relevant outcomes.](image)
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Figure 1 illustrates the complexities of modeling chronic diseases. The main difficulty lies in estimating parameters for such a model from data. In practice, parameters cannot be estimated from a single data set. While one of the biggest strengths of modeling is that parameters estimated from different data sets can be combined, combining results from different studies is not a trivial task. Often the information in available data sources is insufficient to be able to adjust the parameters of interest for the intended model, especially when model parameters are estimated from summary statistics, which is common practice. For instance, standardized mortality rates for chronic diseases (such as diabetes and cardiovascular disease) are often only adjusted for age and gender, and not for other confounders. The difficulty is then to combine summary statistics of different diseases in a multidisease model where one disease might confound the mortality risk of another disease. If models include a direct effect of risk factors on final outcomes, the strength of this indirect effect should be accounted for in modeling the direct effect in order not to exaggerate the total effect (Hoogenveen, Boshuizen, Engelfriet, & van Baal, 2017). A last difficulty in modeling is that chronic diseases often develop over time, as effects of chronic exposure. For many risk factors information on lag-times between exposure and incidence is scarce and thus hard to include in models (Richardson, Cole, Chu, & Langholz, 2011).

Harmonization might also be required before combining different sources of data. For instance, diabetic cases from a data source based on an epidemiological study, where all participants are screened for the presence of diabetes according to World Health Organization criteria, will represent less severe cases of diabetes than those present in data from a hospital registry. This should be taken into account when, for example, applying mortality rates from the second source to cases in the first. Expert judgements usually play an important role in this process of data synthesis. Furthermore, modeling prevalence is tricky, as prevalence is the result of both incoming events (incidence) and outgoing events (death and recovery). For many chronic diseases it is often assumed that recovery cannot be achieved, simplifying the modeling. Inconsistent data on disease-related mortality (survival) and incidence can cause prevalence to explode or implode during simulation. Therefore, accurate and unbiased estimates of incidence and disease-related mortality are needed to obtain sufficiently reliable simulated prevalence rates. As incidence is relatively rare, one needs large epidemiological cohort studies or population registers to obtain accurate estimates. Disease related mortality (survival) is well documented in cancer registries but not for most other chronic diseases. Modeling survival from non-cancer chronic diseases therefore requires additional data collection or analysis. Although it is tempting to use cause-specific mortality for this, for many diseases national mortality statistics strongly underestimate the number of deaths in persons with a particular diseases (Barendregt, Baan, & Bonneux, 2000; Engelfriet, Hoogenveen, Boshuizen, & van Baal, 2011; Sin, Anthonisen, Soriano, & Agusti, 2006; van Baal, Hoogenveen, Engelfriet, & Boshuizen, 2010). For instance, excess deaths in heart failure patients is underestimated by roughly three times when using cause-specific mortality (Engelfriet et al., 2011), and COPD-related mortality is also underestimated when using cause of death assigned in national statistics (Sin et al., 2006). Fortunately, the growing availability in
many Western countries of nationwide linkage of hospital registries or other healthcare-based registries to mortality registrations makes it increasingly possible to obtain high-quality data on disease-related mortality. Furthermore, as prevalence, incidence, and disease-related excess mortality are related, one could also back-calculate the mortality from incidence and prevalence (van Baal et al., 2010). If one assumes that age-specific estimates of incidence and prevalence represent changes an aging individual experiences over time, it is possible to calculate age specific excess mortality rates using the following formula:

\[
\eta(a) = \frac{i(a) - \frac{dp(a)}{da}}{p(a) \times [1 - p(a)]}
\]

where \(\eta(a)\), \(i(a)\), and \(p(a)\) denote, respectively, excess mortality rate, incidence rate, and prevalence proportion at age \(a\). Using regression modeling we can estimate incidence and prevalence as a function of age using cross-sectional or panel data. Excess mortality rates can then be estimated by calculating the change in the prevalence proportion over age \(\frac{dp(a)}{da}\) and applying the formula. Using this incidence-prevalence-mortality (IPM) framework one can also back-calculate prevalence or incidence if data on the other parameters are given (Barendregt, Van Oortmarssen, Vos, & Murray, 2003).

### Simulation Model Types

While there are many different models that simulate the relation between risk factors and chronic diseases, all of these models can be classified into two broad categories of models: state-based models and potential impact fraction (PIF) based models. An important class of models are state-based models, which in health economic applications usually are operationalized as Markov models (Briggs & Sculpher, 1998). In these models individuals can be in multiple states at the same time, for instance a smoker with a BMI of 24 who has diabetes. Such models describe the process of transitions between states, where each individual has a particular transition probability to transit from one state to another in time (e.g., stopping smoking and/or acquiring another disease). When models are formulated in continuous time, transition rates, instead of probabilities, are used. Mostly these types of models are formulated as a Markov model, implying that the probability of moving to another state only depends on the current state and thus does not depend on how the current state was reached (i.e., previous history). Such models are conceptually clear and therefore form the bases of many models in this field. When transition probabilities do depend on history, the relevant aspects of history can be made part of the current state. For instance, when transition to death depends on time since diagnosis, the number of years since diagnosis can be included as characteristic of the current state. State-based models can be implemented in many different ways. When states are discrete (i.e., exposure to risk factors is defined in the form of categories, e.g., smoker vs. non-smoker) and the model is a Markov model, it can be written as a system of ordinary differential equations (ODEs), describing how the number of individuals in each state changes over time.
time. A model simulating such a system of ODEs is usually called a macro-simulation model (see, e.g., Gustafsson & Sternad, 2007). Such a model is identical in formulation to that of a multicompartiment model, with the numbers in each state forming a compartment. Such models are also often referred to as system-dynamic models, where the numbers in each state are the stocks and the transition rates are the flows (see, e.g., Tako & Robinson, 2009).

In the context of chronic disease models, age is an important driver of most transition probabilities. This means that age is an essential part of the state, and the number of states in these models will always be large. Analytical solutions therefore will not usually be feasible, and simulation is required. This can be done by stepping through time and updating the percentage of the population in each state at each time step. However, when the number of states is large, it becomes more efficient to simulate using microsimulation. In microsimulation a large number of individuals is simulated over time. When transition events are relatively rare, this can be done by discrete event simulation, where the time to each possible event is randomly drawn (using the transition probabilities) and the time of the earliest event drawn defines the moment of transitioning to the next state ((Robinson, 2005). At that point a new event is drawn and so on. However, when events are frequent or risk factors take continuous values, as well as when transition probabilities depend on age (or another factor changing with time such as time since diagnosis), microsimulation is better done by stepping through time with fixed time steps while calculating the new state at each time step (also known as “continuous simulation”; Ö zgün & Barlas, 2009). Note that a model simulated with macrosimulation can always also be simulated using microsimulation. Furthermore, approaches can be combined by applying macro- and microsimulation to different parts of the model (Boshuizen et al., 2012). Other approaches to estimate Markov models with many states is to approximate the joint distribution of states by modeling just the marginal distributions (Hoogenveen, van Baal, & Boshuizen, 2010).

In practice, “populating” such state-based models with realistic transition probabilities between all states and the initial distribution over all states is no trivial task. Therefore, despite the conceptual attractiveness of this type of models, there are other types of models that need less detailed information. These important types of models are called PIF-based models. The population to be modeled is divided in age/gender groups, and each group has its own exposure distribution. The exposure distribution is used to calculate the PIF of an intervention. The PIF is calculated as

$$ PIF = \frac{inc_0 - inc_s}{inc_0} = \frac{\sum_{r=1}^{r=n} (p_{0r} - p_{sr})RR_r}{\sum_{r=1}^{r=n} p_{0r}RR_r} $$

where $inc_0$ is the incidence/mortality in the business-as-usual (BUA) scenario, and $inc_s$ in the intervention scenario, $p_{0r}$ and $p_{sr}$ are the proportion of the population in the $r$th exposure state for the BUA and intervention scenario, respectively, and $RR_r$ is the relative risk of those in the $r$th exposure state for a particular outcome. The PIF then is applied to
prevalence rates, mortality rates, and/or incidence rates, as needed by the model. When
the intervention is equal to complete removal of exposure, the PIF becomes the popula-
tion attributable fraction (PAF). The PAF is often used to calculate the impact of expo-
sures. For instance, the Global Burden of Disease study used the PAF to calculate disabili-
ty adjusted life years (DALYs) attributable to risk factors (Forouzanfar et al., 2016). The
PIF or PAF is often used on a cross-sectional population. However, in modeling it can be
extended to repeated applications on consequent years. The difference between such
“longitudinal” PIF-based models and Markov models is that they do not explicitly have a
risk factor state. Therefore selective mortality (individuals with a high exposure will die
more often than those with low exposure) is not included in such models, and the average
exposure of the group does not change due to selective mortality. Instead, these models
require that exposure is externally given to the model for each year in the future.

Linking Models to Economic Outcomes

To estimate economic relevant outcomes such as healthcare spending, labor market par-
ticipation, or quality of life, models such as the one displayed in Figure 1 offer various op-
tions. All these outcome measures can be calculated by being linked to either events and/
or time spent in a state. For certain outcomes, such as medication costs for cardiovascu-
lar disease, it makes sense to link them to time spent in a state as they are prescribed and
taken on a regular bias. For other costs, such as treatment costs after an AMI, it would
make sense to link them to events. Also the event of death is an event to which costs can
be linked. For instance, it is known that healthcare use is centered in the last phase of life
and that this effect differs per disease (Seshamani & Gray, 2004; Wong, van Baal,
Boshuizen, & Polder, 2011). For other outcome measures such as quality of life, the use of
informal care and productivity one faces similar choices. For instance, in terms of labor
market participation one could also make a distinction between the impact of events and
more lasting effects of chronic diseases depending on the disease in question.

Other issues related to multidisease models are connected to the interaction of different
diseases and risk factors. For instance, a relevant question is to what extent comorbidity
influences outcome measures such as healthcare use and quality of life (Barnett et al.,
2012; Hanmer, Vanness, Gangnon, Palta, & Fryback, 2010; Kasteridis et al., 2014); that is,
is the impact of having multiple diseases more or less than the sum of its parts? For
health-related quality of life it has been argued that there is a subadditive effect of dis-
eases so that having two diseases has a less negative impact on quality of life than one
would expect on the basis of the individual diseases (Hanmer et al., 2010). Some studies
have shown that although quality of life decreases as the number of chronic conditions in-
creases, the marginal decrease decreases as the number of conditions increases (Hanmer
et al., 2010). However, they also found that in many cases the quality of life loss caused
by having two diseases was no higher than the loss from having either one of the two dis-
eseases. This latter finding suggests that the disease that leads to most quality of life loss
solely determines the total amount of quality of life loss in patients with multiple dis-
eseases. The same reasoning could apply to the use of informal care, healthcare spending,
and labor market participation. Although research has shown that healthcare use increases with the number of conditions one has, less research has been done on interaction effects between diseases (e.g., Kasteridis et al., 2014).

Finally, while many risk factors are related to a variety of diseases that increase mortality, it is just as crucial to think about the impact life extension may have on several outcomes that go beyond the impact of the diseases that are modeled. More generally, if a person is saved from a premature death due to prevention, this person might develop other diseases. These diseases increase mortality risk, decrease quality of life, and induce healthcare utilization (Fryback & Lawrence, 1997; Rappange et al., 2008). Generally, in simulation models, the impact of these so-called competing risks in life years gained on mortality risk is taken into account. However, the impact of competing risks on other outcomes such as quality of life and healthcare utilization is also important. In the context of economic evaluation, medical costs that are purely the result of life extension are referred to as unrelated medical costs. An example would be costs of treating dementia in life years gained after a lung cancer death is prevented by quitting smoking. It has been shown repeatedly that the inclusion of these costs in economic evaluation is a necessary requirement for efficient use of the healthcare budget (Feenstra, van Baal, Gandjour, & Brouwer; 2008; Meltzer, 1997; van Baal, Meltzer, & Brouwer; 2016). If economic evaluations are conducted from a societal perspective as well, costs of nonmedical consumption (e.g., costs related to housing, Internet, clothing, and food) as well as productivity gains need to be included (Feenstra et al., 2008; Meltzer, 1997). To include future unrelated medical costs, quality of life losses of competing risks, productivity gains, and costs of nonmedical costs, it sometimes suffices in the model to link population averages directly to the projected number of survivors by age (Meltzer, 2012). However, by linking costs and quality of life losses to the event of death one can model the relation between age, healthcare use, and mortality risk and thereby capture the mechanism of postponing death through which health losses and healthcare use are postponed to a later age (Gandjour & Lauterbach, 2005; Gheorghe, Picavet, Verschuren, Brouwer, & van Baal, 2017; Gheorghe, Brouwer, & van Baal, 2015; van Baal et al., 2011). It should be noted that in general, time-to-death is a proxy variable that captures the effects of mainly lethal diseases on healthcare use and quality of life. Therefore, caution must be taken when using time-to-death in a simulation context if some diseases are already included since mixing them may result in conceptually wrong cost-effectiveness ratios and overcorrection (van Baal, Feenstra, Polder, Hoogenveen, & Brouwer, 2011).

Multidisease Models in Health Economics

To gain an overview of current practices in multidisease modeling, several reviews of health economic simulation modeling in the area of public health and prevention were identified (Berg et al., 2017; Berg et al., 2017; Bolin, 2012; Levy et al., 2011; Levy et al., 2011; Squires, Chilcott, Akehurst, Burr, & Kelly, 2016B; Squires et al., 2016B; Weatherly et al., 2009). Although the focus of these reviews was not on how multiple diseases were modeled, several of the conclusions are relevant in the context of this article. First, all re-
views concluded that most models were confined to a narrow perspective in terms of
costing and usually only included healthcare spending related to the diseases that were
included in the model—note that what is considered “healthcare spending” varies from
one jurisdiction to another. Furthermore, while not explicitly mentioned in these reviews,
costs of unrelated medical care in life years gained are often excluded from these models.
Outcomes outside of healthcare such as informal care and productivity gains are usually
also excluded. Second, in terms of outcome measures some reviews have noted that the
use of quality-adjusted life years (QALYs) may not capture all the benefits of preventive
measures and that broader outcomes could be considered. More generally, while the focus
of the reviews was not on how multiple diseases were modeled, all reviews concluded
that the structure, input, and how parameters were developed were often poorly docu-
mented. Also, while these reviews signal differences in costs and outcomes that are
linked to these simulation models, they do not discuss how simulation modeling is done in
practice. Therefore, instead of systematically reviewing multiple models according to a
predefined checklist, this article discusses a few simulation models more in depth—mod-
els that employ various methods that have been applied for multiple applications and
whose technical backgrounds have been published, which allows valid comparisons. The
focus is on a few models for the different approaches discussed in the previous paragraph
and which have served as templates for other models. In comparison with previous re-
views on modeling approaches in prevention, this article focuses on how models accom-
modated multiple diseases in one model and how these were translated into relevant eco-
nomic outcomes.

PIF-Based Models

One of the earliest simulation models that has been used for economic purposes is the
Prevent model (Gunning-Schepers, 1989). A famous publication based on an analysis us-
ing this model showed that preventing smoking might not result in savings to the health-
care system as savings due to the prevention of smoking related diseases are outweighed
by costs in life years gained due to unrelated diseases (Barendregt et al., 1997). The Pre-
vent model is a PIF based model including multiple diseases (e.g., stroke, AMI, several
types of cancers) and risk factors (including smoking and alcohol) that has been used for
different purposes. It uses what it calls a “proportional multi-state lifetable” to combine
effects of multiple diseases (Barendregt, Van Oortmarssen, Van Hout, Van Den Bosch, &
Bonneux, 1998). Next to the PIF the Prevent model also uses a trend impact factor (TIF),
which reflects the impact of autonomous changes in risk factors. The incidence (transi-
tion to the disease state) then is given with:

\[ I = I_0 \left(1 - \prod_r (1 - TIF_r) (1 - PIF_r)\right) \]

Also the PIF can be based not only be based on the exposure in the current year but also
on the exposure in previous years. Lag and latency times can be given that determine
how the PIFs from different years are weighted. In later versions of the Prevent model,
risk factors could also be continuous instead of only categorical. Users can enter their
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own demographic, disease, and risk factor data by providing datasets in the MS Access format, making the Prevent model suitable for many applications. For further details on the model, see Soerjomataram et al. (2011). Time trends in risk factor prevalence need to be provided by the user as Prevent does not explicitly account for the dynamics of the risk factors in relation to mortality so therefore does not model the selective mortality of different risk groups over time. Crucial inputs for each disease are incidence, prevalence, and disease-specific mortality. Usually, data for risk factors is derived from health surveys and/or epidemiological cohort studies while disease input comes from various sources such as cancer registries and causes-of-death registrations. Disease-specific mortality needs to be derived using incidence prevalence mortality modeling (Barendregt et al., 2003), as otherwise disease prevalence might “explode” or “implode” during simulation. Disease prevalence depends on risk factors, as relative risks (derived from epidemiological studies) in combination with risk factor prevalence determine disease incidence rates. Prevent also has options to model disease-related mortality without modeling the associated prevalence. Costs in the Prevent model are calculated by linking disease-specific per capita costs by age and gender to prevalence predictions of the epidemiological model.

Costs of diseases that are not explicitly modeled (i.e., costs of future unrelated care) by Prevent are calculated by multiplying the projected number of survivors times per capita costs by age, excluding the costs of the diseases already modeled. A similar approach as with costs is used to calculate QALYs/DALYs with Prevent—disability weights from burden of disease studies are linked to disease prevalence estimates while quality of life losses due to diseases not modeled are incorporated by linking an “other causes” disability weight by gender and age. These are also derived from burden of disease studies. The first incarnation of the Prevent did not include QALY-type outcome measures, but later versions used disability weights from the Global Burden of Disease study linked to prevalence estimates to calculate summary measures of population health combining the impact on length and quality of life. This is usually done assuming an additive effect of diseases on quality of life and by also including an “other cause” disability weight accounting for the fact that quality of life decreases at older ages because of diseases not explicitly modeled.

The original Prevent model was developed for the Netherlands and has been used for forecasts of population health/healthcare needs and cost-effectiveness studies. However, the structure of the Prevent model has been influential for many other models and has been adopted by several models in Australia and New Zealand, which are used in assessing the cost-effectiveness of preventive interventions targeting a variety of risk factors (Blakely et al., 2015; Carter et al., 2008; Cobiac, Vos, & Barendregt, 2009). In some applications these models incorporated time trends in the transition rates between different states (Blakely et al., 2015). The cell-based version of the IMPACT coronary heart disease (CHD) mortality model, developed by Capewell and colleagues, is based on similar PIF methodology (Bennett et al., 2009) and implemented in Excel. The IMPACT model is used to estimate the fraction of deaths prevented or postponed over a specified time period that is due to either risk factor trends or changes in treatment. Another model inspired by the Prevent model that has been developed fairly recently is the Sheffield Alcohol Policy
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Model (SAPM; Brennan et al., 2015; Brennan, Meng, Holmes, Hill-McManus, & Meier, 2014; Purshouse, Meier, Brennan, Taylor, & Rafia, 2010). This model, implemented in Microsoft Excel VBA, has been used in several policy relevant applications for the United Kingdom. The model makes a distinction between mean weekly alcohol consumption and peak alcohol consumption (e.g., binge drinking). Mean weekly alcohol consumption is linked to the prevalence and mortality of 47 chronic diseases through potential impact fractions. In contrast with the Prevent model, mortality is not a function of prevalence as it is modeled separately in the SAPM model. Similarly to the Prevent model, the SAPM does not explicitly account for the dynamics of the risk factors in relation to mortality, and so it does not model the selective mortality of different risk groups over time. While the model has a broad range of outcomes (e.g., labor market participation, alcohol tax revenue, crime and traffic accident harm), many of these outcomes are not linked to chronic disease but directly to peak alcohol consumption. This makes sense in the case of alcohol, where peak consumption has an independent effect on these outcomes. Healthcare cost calculations are also done directly on spending by disease using attributable fractions. Although a broad range of outcomes are considered, healthcare spending caused by increased life expectancy for diseases not causally related to alcohol consumption are not included, which is in accordance with the guidelines of economic evaluation in England (Morton et al., 2016).

State-Based Models

Another early influential simulation model that is still being used is the CHD Policy Model (Weinstein et al., 1987), implemented in Fortran 95. It uses prediction equations based on the Framingham study to model a sequence of coronary events, including model states for Angina, AMI, sudden death, and post-myocardial infarction, as well as states for individuals receiving particular treatments (e.g., coronary artery bypass grafting and percutaneous coronary intervention), which depend on risk factors such as smoking, total cholesterol, diastolic blood pressure, and body weight. The model is based on a macro-simulation approach simulating the number of individuals in strata of age, sex, and broad risk factor categories. Scenarios that affect continuous risk factors like blood pressure and cholesterol are modeled by changing the average value of blood pressure or cholesterol within each risk factor category. Incident cases are entered first in a “bridge” model, modeling acute illness and linking the disease-free population to the chronically ill population. The bridge model simulates events during the first 30 days of disease. Each possible path through this bridge period is assigned costs based on published sources of cost data. Survivors then enter a disease history model where the state depends on previous CHD events experienced and which further CHD events or treatments such as bypass surgery can occur. In this part of the model, costs are attached to events (like a myocardial infarction of bypass surgery). This model has been used to evaluate the cost-effectiveness of interventions for primary and secondary prevention of CHD as well as for population health forecasts (Mekonnen et al., 2013; Moise et al., 2016). Next to the original model populated with data from the United States, there are also versions targeting Argentina and China (Moran et al., 2008; Moran et al., 2011). Quality of life weights in this
model are not derived from the global burden of disease study but from the Beaver Dam health study (Fryback et al., 1993). In comparison with other models, the CHD models costs in more detail by linking costs not only to prevalent cases but also to specific events. In some applications of the model, healthcare costs of diseases not explicitly modeled in life years were included (Prosser et al., 2000).

A model that contains elements from both the Prevent model as well as the CHD policy model is the RIVM-Chronic Disease Model (CDM; Hoogenveen, van Baal, Boshuizen, & Feenstra, 2008; Hoogenveen et al., 2010), implemented in Mathematica and later in R. The CDM is a tool to describe the morbidity and mortality effects of risk factors (including smoking and overweight, physical activity, alcohol) for chronic diseases (including AMI, stroke, heart failure, diabetes, and several types of cancer) in the Dutch population and has been used for projections of risk factor and disease prevalence and cost-effectiveness analysis (Feenstra, van Genugten, Hoogenveen, Wouters, & Rutten-van Molken, 2001; Kanters, Brouwer, van Vliet, van Baal, & Polder, 2013; Struijs et al., 2005). The CDM has a flexible model structure, and risk factors and chronic diseases can be selected depending on the research question. The CDM is in concept a Markov model, but some approximations are used that make it possible to update the marginal frequencies of both diseases and risk factors, without explicitly modeling all separate states (Hoogenveen et al., 2010). That is, the model updates the percentage of smokers and percentage of those with a particular disease at each time step, without explicitly calculating the number of individuals in each combination of smoking class and disease state. This not only makes for fast and feasible simulation, even with many risk factors and diseases, but also secures that only marginal data on risk factors and diseases are needed. Initial distributions over all states are calculated using similar data and assumptions to the Prevent model and the modeling of CHD is similar to the CHD model. Crucial ways in which the CDM is different from the Prevent model are that the CDM is a Markov model requiring transitions between all states and that comorbidity between diseases caused by shared factors is explicitly accounted for in the calculation of the initial distributions. Crucial inputs for each disease are incidence, prevalence, and excess mortality rates by age and gender. Excess mortality is defined here in a similar fashion as in a simple one disease IPM model, indicating the difference in mortality between persons with and without a particular disease. However, in general only part of this excess mortality can be attributed to the specific disease, and the difference between the excess mortality and the part uniquely attributable to the disease can be interpreted as mortality due to comorbid conditions. The mortality due to comorbid conditions is especially important at higher ages, such as for COPD, for which smoking—which has many other related chronic diseases—is an important risk factor. Therefore part of the COPD excess mortality must be attributed to other smoking related diseases (e.g., CHD and lung cancer). Using data on the clustering of diseases pairs, the CDM translates excess mortality rates into so-called attributable mortality rates (Hoogenveen et al., 2017). Again, these corrections depend on the risk factors and diseases selected. Also note that the CDM allows for a direct effect of risk factors on mortality, which becomes smaller the more diseases are selected. To estimate incidence, prevalence, and excess mortality rates for all diseases in the general population, Dutch
population data from general practitioner registrations, hospital and cancer registries, and health surveys are used. Relative risks are based on meta-regressions, and data on risk factor prevalence and transitions are based on health surveys and epidemiological cohort studies. In terms of costing, the CDM only includes healthcare spending based on data from the Dutch Cost of Illness study (including spending on long-term care; see https://www.volksgezondheidenzorg.info/cost-of-illness) and uses a similar approach to the Prevent model by linking prevalence estimates to costs per patient (van Baal, Feenstra, Polder, Hoogenveen, & Brouwer, 2011). More recently, a distinction has been made between costs in the last year of life and other years (conditional on age and gender). Health effects in the CDM are expressed in QALYs using disability weights from the Dutch Burden of Disease study, which are linked to disease prevalence (van Baal, Feenstra, Hoogenveen, de Wit, & Brouwer, 2007). For diseases not explicitly modeled in the CDM, disease prevalence from the Dutch Burden of Disease study is used by age and gender and assumed constant (Melse, Essink-Bot, Kramers, & Hoeymans, 2000). Disability weights for comorbidity are defined assuming a multiplicative adjustment method (van Baal, Hoeymans, Hoogenveen, de Wit, & Westert, 2006). The epidemiological structure of the CDM has been used as a starting point for the DYNAMO-HIA (A Dynamic Model for Health Impact Assessment) model (Boshuizen et al., 2012; Lhachimi, Nusselder, Boshuizen, & Mackenbach, 2010), which is programmed as partial microsimulation model in JAVA. This implies that only risk factor development over time is modeled through microsimulation. The development of disease is simulated by constructing a proportional multistate life table for each simulated individual. This reduces the amount of Monte Carlo variation in the simulation, making for a more efficient simulation.

Due to increases in computing power, in recent years the number of microsimulation models has been growing. An early model in this area is the Population Health Model (POHEM) developed in the early 1990s by Statistics Canada (Hennessy et al., 2015; Wolfson, 1994), implemented in MODGEN, a generic microsimulation programming language supporting the creation, maintenance and documentation of dynamic microsimulation models. In the POHEM model an initial population is derived from a survey population, or, alternatively, a synthetic population is constructed by letting the model run from 1971 to the starting moment. In the latter method, however, the lack of historical information on, for instance, smoking behavior is a challenge. Empirically derived prediction algorithms and risk factor transition rules are applied to this population (Hennessy et al., 2015). Like in the previous models, the application of incidence and disease-related mortality can lead to unrealistic prevalence rates. In POHEM this is tackled by applying calibration, by comparing the population after a one-year update with expected outcomes based on observed data and iteratively adjusting the prediction algorithm until the simulated data match the observed data. The model can include a utility score, the Health Utility Index Mark 3, from a prediction model for this utility based on survey data. In the osteoarthritis model, for instance, this utility score is assigned based on osteoarthritis status, age, sex, and BMI (Kopec et al., 2010). Healthcare costs are added to the model by adding health expenditure data on an individual level, drawing the probability of specific surgery, in-
including a duration of hospital stay, as well as by adding average annual costs, depending on age, sex, and stage of disease (Amankwah et al., 2017; Sharif et al., 2015).

A more recent microsimulation model was developed by UK Health Forum. Originally the model was developed to explore the future disease burden by obesity (Butland et al., 2007), implemented in C++. In the last decade, it has been extended to other countries (Webber, Kilpi, Marsh, Rtveladze, McPherson, et al., 2012; Webber, Kilpi, Marsh, Rtveladze, Brown, et al., 2012) and—as part of the ECONDA project—used for estimating the cost-effectiveness of interventions for chronic disease prevention, screening, and treatment (Divajeva et al., 2014). Incidence of disease is based on relative risks, and calibration is used to obtain incidence rates that agree with observed data. In this work, utility weights were added to individuals dependent on disease stage, with utilities of disease-free individuals probably being 1 (not explicitly stated). Healthcare costs are estimated by multiplying the number of individuals with a disease with the annual healthcare costs per patient, estimated from different sources. Costs of diseases not explicitly modeled are not included.

**Conclusion**

This article has discussed several methodological issues related to the economic modeling of multiple-chronic diseases related to risk factors. There is a distinction between conceptual issues related to the construction of the epidemiological simulation model and issues related to linking outcomes of the epidemiological simulation to economic relevant outcomes. Based on this distinction, several models link risk factor to multiple chronic diseases in order to explore how these issues are handled in practice. Furthermore, the article discussed several model types that can be used to model multiple chronic diseases. To illustrate how models deal with the issues identified, several simulation models were discussed in depth.

With regards to epidemiological modeling, most models used relative risks from epidemiological studies from various countries (often from meta-analyses) and linked these to chronic disease incidence, prevalence, and/or mortality derived from national data sources. Models differed to what extent they modeled the dependencies between incidence, prevalence, and mortality. Some modeled prevalence and mortality independently, while in other models risk factors influenced mortality only through its increased risk on acquiring a disease, which in turn influenced mortality. Some models combined both: where increased mortality risk from a risk factor runs both via diseases and via a direct route of increased risk of mortality. More generally, models differed in to what extent consistency between different parameters was built into the model. For instance, all models modeled the causal influence of risk factors on disease, but not all models modeled the reverse mechanism—in the sense that risk factor distributions change due to selective mortality (e.g., the prevalence of smoking decreases at higher ages because smokers die younger on average). Modeling parameters such as prevalence, mortality, and costs separately definitely has its advantages. However, modeling the dependencies between the pa-
parameters forces the researcher to think carefully about consistencies between different parameters and data sources. Such consistency checks between parameters can also be seen as a form of model validation. Multimorbidity was not always explicitly modeled; in some cases diseases were modeled separately assuming independence. Sometimes cause-specific mortality rates were used to model the additional mortality risk as a result of having a chronic disease. However, this might not be most appropriate in the context of a Markov model (Engelfriet et al., 2011). In terms of computation, some models used a Markov approach numerically simulated either using macro- or microsimulation. Other models were not of the Markov type but based on epidemiological methods such as population impact fractions. Another observation is that when describing modeling results from the literature, some details of the modeling are often unclear from the description in scientific papers. The descriptions often convey the general approach but not in enough detail to reproduce the calculations. More guidelines for reporting and warranting of reproducibility are needed.

In terms of economic relevant outcome measures, all models focused on healthcare spending as an outcome, and all models included the costs of diseases in the model. Most models simply linked a prevalent case of disease to annual patient cost, although some models linked specific treatments or events to costs. Few models combined both approaches (annual costs for continuous care with peak costs surrounding specific events). Many models also included costs of unrelated diseases by linking them to per capita costs by age and gender. All models assumed that costs are additive and did not assume any interactions. This may have to do with the fact that costs are mainly derived from top-down costs of illness studies in which costs are uniquely attributed to diseases. Costs outside the healthcare sector such as productivity gains and costs of nonmedical consumption were not included in the models discussed here. All models allowed health benefits to be expressed in measures combining length and quality of life. Often, this was accomplished by coupling disability weights from burden of disease studies to predictions of the simulated model. Some models used a multiplicative model to capture the impact of multiple diseases on quality of life, thereby assuming that the impact of having multiple diseases on quality of life is less than the sum of its parts.

The methodological issues discussed in this article closely relate to concepts that have been discussed in the area of model validation (Kopec et al., 2010; Philips et al., 2004). For instance, Kopec et al. consider model validation broadly as the process of gathering evidence in support of the model’s intended use and give three elements:

1. the process of model development: conceptual model, data sources of parameters, computer implementation (including testing procedures to verify computer code);
2. the performance of the model: face validity (plausibility), internal consistency, parameter sensitivity, cross-validation (between-model comparisons), and external validation (comparison with external data); and
3. the quality of decisions based on the model.
This article discussed issues related to the first two elements. What is crucial in addressing the methodological issues highlighted in this article is that a conceptual model is developed and translated to statistical analyses that allows identification of relevant parameters. When consulting with subject-matter experts, it is not unusual to end up with a conceptual model that contains more parameters than are identifiable from existing data sources. The process of scaling down the conceptual model to one that both has identifiable parameters and still captures the essential features of the problem can be a challenge. Note that in the type of modeling discussed here, comparing the outcome of a model with observed data is often not an option, especially when the outcomes modeled are in the far future or when the model is already calibrated against the best available data.

This article did not explicitly discuss issues related to uncertainty analyses. As model parameters are often uncertain, some form of uncertainty analysis is required, that is, an assessment of how the uncertainty in the parameters influences the outcomes of the model (Bilcke, Beutels, Brisson, & Jit, 2011; Briggs et al., 2006; Claxton et al., 2005). Sometimes this is also referred to as sensitivity analysis; however, the term “sensitivity analysis” is more often used to refer to the influence of higher level modeling assumptions, also referred to as “model uncertainty” or used for the act of analyzing how and why assumptions (of the model structure or the parameters) influence the outcome. Parameter uncertainty is most easily assessed using probabilistic uncertainty analysis: instead of having a fixed value, each parameter is assumed to have a distribution (which are sometimes correlated), reflecting the uncertainty of the parameter. In general, many of the simulation models discussed were originally developed using fixed parameter values, but over time more and more parameters of these models have been modeled as coming from a distribution. Model uncertainty is less easily ascertained. Hendriksen et al. (2017) incorporated features of other disease models that modeled effects of salt in their own model in order to study effects of structural differences. However, this was only possible for a subset of all differences between models. In cross-validation studies, models are compared using the same data. Such exercises have been carried out in the area of diabetes modeling and COPD modeling (Hoogendoorn et al., 2017; Palmer, 2013). Such studies can be regarded as a sensitivity check for model structure.

With advances in computer power and tools and increasing availability of claims and registration data, the field of multidisease modeling is expanding. There are models that are made and used for a single application, as well as models that evolve from one application to the other. The use of simulation modeling facilitates a better understanding of the impact of healthcare interventions on a broad range of outcome measures including healthcare use, quality of life, and mortality. Consequently, the use of simulation modeling may help inform healthcare decisions related to the consequences of population aging. While the literature on methodological issues for such models are scattered over different scientific disciplines and their associated journals, some important methodological challenges have been addressed. Nevertheless, models differ significantly in the amount of detail with which disease processes are modeled, as well as in the way costs are linked to epidemiological outcomes. This might be explained by the fact that in comparison with
the modeling of infectious diseases or the modeling of clinical interventions for cost-effectiveness purposes, there is little guidance on simulation modeling for multiple chronic diseases related to risk factors. Recently, guidance has been issued on how to develop the structure of public health economic models (Squires et al., 2016A). However, in that guidance the focus was not on how parameters can be estimated from multiple data sources and combined in a consistent manner.

In terms of future research, two areas are of particular interest. First, more research could be devoted to model comparisons, as in the cross-validation studies described here. Such validation studies can yield important insights and can be seen as a sensitivity check. Another area of future research would be to invest more in the connection of multidisease models to econometric research. Simulation modeling of multiple diseases would be an ideal field for bridging the worlds of epidemiological modeling and empirical economic research related to aging. While important steps have been made such as linking the research on time to death and HCE to such models, linking broader outcomes such as labor market participation and the impact of disease on nonmedical consumption to multidisease could increase the policy relevance of these models.

Further Reading


Modeling Chronic Diseases in Relation to Risk Factors


References


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