Short and long-term consequences of coronary heart disease
Application of register based data in economic evaluations

PhD-thesis

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Short and long-term consequences of coronary heart disease –

Application of register based data in economic evaluations

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Preface

This PhD-thesis finalises the research I embarked on in 2006, while I was working at the National Institute of Public Health and enrolled as a PhD-student at the University of Copenhagen. During the first months of the project, the National Institute of Public Health merged with the University of Southern Denmark as a result of the government globalisation strategy. While this merger had only minor consequences for most individuals involved, it became a major advantage for me. I maintained my position at the National Institute of Public Health while I changed my PhD enrolment to the University of Southern Denmark, faculty of health sciences, which became the base for me during the last two and a half years of this study.

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Summary

Coronary heart disease (CHD) is a serious, chronic and potentially fatal condition, which has consequences at multiple levels. For the individual who experiences a CHD event, consequences in the short term include changes in mental health, in social life and in lifestyle. In the longer term, the individual’s labour market affiliation may be affected, as well as their earnings and consumption. As consequence of the disease, heart patients may often change lifestyle and thereby reduce the negative impact of the disease, and in the long term reduce the morbidity of CHD and other diseases.

At the health care sector level and at the societal level CHD also has an important impact. Aside from being the most frequent cause of hospital admission, CHD also causes changes at societal level, such as changes in patients’ labour market affiliation and future earnings and consumption.

The main focus of this assessment of the short and long-term consequences of coronary heart disease is the economic evaluation of health care and health promotion interventions. Economic evaluations are frequently based on data derived from randomised controlled trials which often apply a rather short study time frame. In this thesis I argue that the time perspective of economic evaluations should be long enough to be able to capture all relevant costs and effects. I also argue in favour of including other types of data sources than those available from RCT-based data: such as long-term data from clinical and administrative registers.

This thesis is based on four studies: paper 1 considers the health care costs of CHD and possible impacts of lifestyle interventions that may prevent CHD. We found that CHD is associated with a statistically significant increase in health care costs and that amongst people at risk of developing CHD, an unhealthy life style is associated with higher health care costs than for people with a healthy lifestyle.

Paper 2 is an assessment of the longer term labour market consequences of CHD. We compared labour market affiliation of CHD patients with a reference group of individuals with similar age, gender and socio-economic characteristics in a duration analysis covering up to 23 years. The analysis showed that CHD patients withdraw from the labour market on average 0.8 year earlier than individuals in the reference group.

Paper 3 is an economic evaluation of a newer treatment strategy (drug-eluting stents) for CHD. The study used register-based data to assess the long-term cost-effectiveness of the intervention. We found that the
incremental cost-effectiveness ratio was advantageous to drug-eluting stents after five years; however no firm conclusions on cost-effectiveness could be made based on this analysis since the observed difference in health outcomes was rather small.

Paper 4 comprises an empirical assessment of the inclusion of survivor costs in the economic evaluation. Using register-based data for the entire Danish population, we derived age specific figures for both production and consumption with a view to including such figures in cost-effectiveness analyses. This paper contributes to the ongoing debate on inclusion of survivor costs by providing empirical figures on the magnitude of survivor costs.

Overall, I found that the best available data should be used for analysing long-term costs and effects of interventions in the field of preventing and treating CHD. For this assessment, register-based data was used due to the applicability of results and the time frame of the analysis. The four papers demonstrate that there are important resource consequences of CHD in both the short and the long-term.
Danish summary

Iskæmisk hjertesygdom (CHD) er en kronisk, alvorlig og potentielt livstruende sygdom, som har omfattende konsekvenser på flere niveauer. Først og fremmest sygdomskonsekvenser på det individuelle niveau, herunder sociale og psykologiske konsekvenser på kort sigt og økonomiske, blandt andet arbejdsmæssige, konsekvenser på længere sigt. Sygdommens opståen kan endvidere forårsage ændringer i livsstil, der kan påvirke forekomsten af andre livsstilsrelaterede sygdomme.

I sundhedsvæsenet er der betydelige konsekvenser af CHD: En forholdsvis stor andel af de samlede sundhedsomkostninger vedrører behandling af CHD, og mange forebyggelses tiltag retter sig mod CHD og andre livsstilsrelaterede sygdomme. På samfunds niveau, dvs. uover sundhedsvæsenet, påvirker CHD patienternes arbejdsmarkedstilknytning, ligesom sygelighed og dødelighed har betydning for fremtidigt forbrug, både indenfor og udenfor sundhedssektoren. Ændringer i produktivitet og forbrug har konsekvenser uover det individuelle niveau.


Denne afhandling er baseret på fire videnskabelige artikler. Artikel 1 omhandler sundhedsomkostninger associeret med CHD og med en uhensigtsmæssig livsstil, med henblik på at kunne vurdere effekten af eventuelle forebyggende tiltag. Vi fandt, at sundhedsomkostningerne var statistisk signifikant højere for hjertepatienter end for ikke-hjertepatienter. Desuden fandt vi, at sundhedsomkostningerne blandt personer i risiko for at udvikle CHD var lavere for personer med sund levevis end med usund livsstil.

Artikel 2 er en analyse af arbejdsmarkedskonsekvenser af CHD på kort og langt sigt. Vi sammenligne arbejdsmarkedstilknytning blandt hjertepatienter med en referencegruppe af ikke-hjertepatienter, der var identiske med hjertepatienterne med hensyn til køn, alder og socioøkonomiske karakteristika. Vi analyserede arbejdsmarkedstilknytning over en periode på op til 23 år ved brug af overlevelsesanalyse og fandt, at hjertepatienterne forlod arbejdsmarkedet 0,8 år tidligere end personer uden CHD.
Artikel 3 er en økonomisk evaluering af en nyere, meget udbredt behandling af CHD, drug-eluting stents, der anvendes ved ballonudvidelse af forsnævrede koronararterier. Vi brugte registerdata og kunne dermed analysere omkostningseffektivitet på væsentligt længere sigt end hovedparten af tidligere studier på området. Vi konkluderede, at drug-eluting stents var omkostningseffektive efter en fem-årig periode, om end der ikke kan drages håndfaste konklusioner på basis af resultaterne, da forskellen i effekt mellem de to sammenlignede interventioner var ret lille.

I artikel 4 anvendte vi registerdata til at beregne produktion og forbrug i et-års aldersklasser. Disse opgørelser kan anvendes som udtryk for de fremtidige økonomiske effekter af overlevelse. Beregningerne kan anvendes i økonomiske evalueringer ved inddragelse af fremtidige omkostninger. Artiklen bidrager til debatten om inklusion af fremtidige omkostninger i økonomiske evalueringer af sundhedstiltag ved at demonstrierre effekten af at inddrage disse i økonomiske evalueringer.

Jeg konkluderer at økonomisk evaluering skal inddrage de bedste data der er til rådighed. Jeg har anvendt register-data til at analysere interventioner der har til hensigt at behandle eller forebygge CHD, idet analysen derved fik en længere tidshorisont og resultaterne fik en øget anvendelighed. De fire artikler viser at der er store ressourcemæssige konsekvenser af CHD, både på det korte og det lange sigt.
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<td>Cost benefit analysis</td>
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<td>CEA</td>
<td>Cost-effectiveness analysis</td>
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<td>CHD</td>
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<td>COI</td>
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<td>CV</td>
<td>Compensating variation</td>
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<td>DANCOS</td>
<td>Danish national cohort study</td>
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<td>DRG</td>
<td>Diagnosis related groups (hospital tariff system)</td>
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<td>EQ-5D</td>
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<td>HUI</td>
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<tr>
<td>ICD</td>
<td>Implantable cardiac defibrillator</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>LY</td>
<td>Life years gained</td>
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<td>NICE</td>
<td>National Institute of Clinical Excellence (UK)</td>
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<td>NHIS</td>
<td>National health interview survey</td>
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<tr>
<td>NHS</td>
<td>National Health Service (UK)</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<td>US Panel</td>
<td>Recommendations on cost-effectiveness analysis</td>
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<td>WTA</td>
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I. Introduction

Coronary heart disease (CHD) is one of the most important causes of death and hospitalisation in Denmark as well as in most other countries. In addition, a variety of health care and health promotion interventions aim at treating, alleviating or preventing CHD. When analysing the resource consequences of CHD, it appears that there are significant consequences in both the short and the longer term.

In health sciences, costs and effects of interventions as well as costs of an illness are often assessed over a short time period. Frequently, the effect of a health care intervention is measured in randomised controlled trials (RCTs) with a restricted time frame of e.g. six months or one year.

The short-term consequences of CHD have been widely assessed, using RCTs and other data sources\textsuperscript{1-9}. However, only few studies\textsuperscript{10-12} have considered costs and consequences beyond the first year.

Use of register-based data allows for analysis of a longer time period, which may alter results substantially. In addition, register-based data can provide information of a different quality than trial data, for use in cost-effectiveness analysis. For chronic conditions such as CHD, disease progression, lifestyle changes, and decisions related to the condition, such as labour market withdrawal, may occur at a much later stage than one year\textsuperscript{13}.

Over a longer time period important costs and effects may arise both within and outside the health care sector, pointing to the significance of the perspective of the analysis. In addition, using perspectives narrower than that of the entire society for economic evaluation excludes important costs and consequences and may lead to inefficient resource allocations\textsuperscript{14}.

The main focus of this thesis is analysis of the costs and consequences of coronary heart disease, making the case for increased use of register-based data, inclusion of a sufficient time frame and adoption of the societal perspective.

This thesis is structured as follows: First the overall research question is formulated and motivated. Chapter II describes the theoretical rationale for the assessment of costs and consequences in economic evaluation
and outline some of the key issues in identifying costs and effects in economic evaluation. In Chapter III, I assess and discuss the types of data sources that are applied in economic evaluations and focus on their advantages and disadvantages in particular when the long-term perspective is involved. Chapter IV provides a literature review of economic evaluations within the field of coronary heart disease, focusing on the perspective and time frame applied as well as the types of data sources used. In chapter V, I describe the methods and data sources used in the four papers, relating these to the main points of the preceding chapters. Chapters VI through IX list the main points from the four papers in the thesis. The four papers are attached as appendices. Chapter X concludes on the main themes of the thesis.

Overall research question

Coronary heart disease is one of the leading causes of death and hospitalisation throughout the Western world. In Denmark, the mortality from CHD was 317 per 100,000 men and 333 per 100,000 women in 2005. Also, CHD was the most frequent cause of hospitalisation in Denmark with 1,786 admissions per 100,000 men and 1,409 admissions per 100,000 women in 2005. Aside from the serious disease consequences such as hospitalisation or death, a number of other consequences follow a case of CHD. Hence, I focus on consequences in different time frames, where the short-term comprises the first year following an event, and the longer term reaches beyond this horizon. I also consider different perspectives of consequences, in particular the health care sector and the societal perspective.

Short-term consequences of a CHD event comprise changes in the individual’s mental health, social life and lifestyle. In the longer term, the individual’s labour market affiliation may be affected, as well as their earnings and consumption. Since a heart patient’s lifestyle often improves as a consequence of disease, long-term morbidity may also change.

Aside from individual consequences, morbidity and mortality from CHD also affects the societal level. In the short term, CHD impacts on health care costs related to CHD treatment, while in the longer term other health care costs could change. In addition, changes in patients’ labour market affiliation, earnings and consumption cause changes at the societal level.

The consequences of CHD are thus fourfold: Consequences for the individual in the short-term, consequences for the individual in the long-term and societal consequences in the short and long-term. All four dimensions include medical, economic and other consequences. Assessment of the variety of
consequences is important when analysing costs and effects of health care and health promotion interventions.

The first key issue of this thesis is the importance of including long-term consequences in the economic evaluation of health care interventions. Focus on the short-term alone could lead to ineffective decisions as future costs and effects may be significant. For health care interventions, the time frame of the analysis should be sufficient to capture all relevant costs and effects. In health promotion, costs appear both in the short-term as directly related to the intervention, and in the long-term, as savings resulting from improved health and longevity.

The second and third key issues relate to the first. As register-based data often cover a longer time span than trial data, register data may be as applicable for use in economic evaluations as trial data. The real world applicability of register-based data provides another central argument for use of these data.

Thirdly, an expanded time frame of analysis necessitates inclusion of consequences beyond the health care sector perspective. Decisions based on an analysis applying a perspective that is narrower than societal, could lead to inefficient resource allocations.

The principal motivation for this thesis then becomes: identification of the best available data and the most appropriate time frame and perspective for the economic evaluation of health care and health promotion interventions, focusing on prevention, treatment and rehabilitation of coronary heart disease.
II. Methods for economic evaluation

Economic evaluation of health care interventions comprises analysis of economic and other consequences of disease and usually compares two or more treatments of a particular disease or disorder. This chapter outlines the theoretical rationale for economic evaluation and some of the most widely used methods.

Economic evaluations of health care interventions most often take the form of cost-effectiveness analyses (CEA). In CEA costs associated with different interventions are related to the effects of the interventions. Effects are measured as life years gained, quality-adjusted life years (QALYs) gained, or in a few cases a more clinical measure such as decreased blood pressure.

Cost-benefit analysis (CBA) differs in nature from CEA as benefits in CBA are measured in monetary terms. In CBA, net benefit is obtained by subtracting the costs from the monetary value of the effect. Willingness to pay (WTP) estimates are most often used as the monetary value of the effect of the intervention. The use of CBA in the field of health care is rather limited, but as CEA derives from CBA, the theoretical foundations of CBA is outlined below. Further, the main elements of economic evaluation are defined. I will describe the process of identification of costs and effects and some key issues of these processes, as well as argue for the importance of including long-term costs and effects. This chapter also introduces some of the existing recommendations for CEA, including the 1996 US Panel reference case. Finally, I will briefly discuss the topic of cost-of-illness analysis (COI).

The rationale of CBA and CEA

CBA rests on traditional welfare theory, while CEA is not as closely linked to welfare theory. Traditional welfare theory is mainly concerned with the societal desirability of different resource allocations. Society is defined as a group of individuals and the societal welfare function can be defined as some form of aggregation of each individual’s welfare. The recommended societal perspective for economic evaluations derives directly from the notion of societal welfare.

It is assumed that individuals seek to maximise their own utility subject to a budget constraint which is determined by their income. In a group of individuals, such as a society, welfare is a function of the individual utilities. In the following, the utility from health is used as an example of individual utility.
The individual utility from health can be expressed as a function of income and conditions influencing on utility or the health state. The individuals will aim for the health state that maximises their utility subject to the budget constraint given by their income. In a group of individuals, utility functions are not comparable because different individuals may assign different value to health. Therefore utility maximisation in a society, where more than one individual is involved, becomes challenging. For two or more people, a distribution of goods is said to be Pareto efficient when one individual cannot increase her utility without making the others worse off. A Pareto improvement occurs when one individual increases her utility while the other individual's utility is unchanged or improved\textsuperscript{25}.

The concept of Pareto efficiency appears rather restrictive. Most redistributions of income and consumption are likely to make some individuals worse off. Redistribution of income takes place at the societal level in the form of taxes and distribution of public goods and services such as health care. Pareto efficiency does not ensure a fair income distribution; in fact a very unequal income distribution can be Pareto efficient\textsuperscript{25}. Based on the recognition that some individuals may have access to plenty of commodities but may not need that much, while other individuals may need more than they have access to, the notion of compensating was introduced\textsuperscript{25}. Some people may be healthy and need only little health care while having access to more health care than they need. For others the situation is the reverse and therefore they will be interested in trading with those individuals having an abundance of health care.

The Kaldor-Hicks compensation criterion defines a situation as being efficient if those benefiting from the change in distribution can fully compensate those losing, and still experience a benefit. For each individual, the utility as a function of income minus a compensating variation (CV) and the changed characteristics of the health state should equal the utility of the income and characteristics of the former situation. CV could be positive, if the new situation implies an improvement for the individual. CV then represents the individual’s willingness to pay (WTP) for the improved health state. For deteriorations in health, CV would be negative and the interpretation of CV is the willingness to accept (WTA – an income gain) the deterioration in health. The new situation is considered optimal according to the Kaldor-Hicks criterion, if the sum of compensating variations over all individuals exceeds zero\textsuperscript{25,26}.

The Kaldor-Hicks compensation criterion is hypothetical rather than actual; in other words if the compensation can take place hypothetically, the new situation is efficient. From the equation of
compensating variation, the rationale for cost-benefit analysis can be derived directly \(^{22,26-28}\). The difference in preferences between the new and the former health state is expressed in monetary terms, via the WTP or WTA \(^{25}\). This constitutes the benefit of the new situation and is used to compute net benefit by subtracting costs. The cost-benefit equation expresses the net benefit as benefits minus costs.

The Kaldor-Hicks compensation criterion and its application in health care are based on the rather rigid assumption that all individuals in the society have identical marginal utilities of income \(^{25,29}\). Whereas utilities as such are not added or compared across individuals, the monetary expression of their preferences are added and assumed of equal value. The implication of this is that the rich and the poor should place the same utility on a marginal change in income. Therefore compensation using the monetary terms of cost-benefit analysis is based on an assumption that may not be fulfilled, which is the rationale for deviating from the monetary expression of benefits. A less theoretical motivation is the technical and practical difficulties in expressing benefits in monetary terms within health \(^{22,30}\).

In cost-effectiveness analysis, effects are not measured in monetary terms. Effects or outcomes of health care interventions usually express a health gain. The deviation from monetary expression of benefits also makes the connection to traditional welfare theory unclear \(^{25,28}\). Instead of subtraction, CEA uses division to express the cost per health gain \(^{27,31}\). In addition, CEA maximises societal welfare subject to a budget constraint, whereas CBA maximises net (monetary) benefit. The presence of a budget constraint also represents an important difference between CEA and CBA. Further, as economic evaluation is used for decision making, the results should relate to what the health gain is worth \(^{20}\). In CBA, the value of the intervention is produced by the CBA-figure while for CEA the results need to be compared to a threshold or a league table \(^{32}\) in order to conclude on the value \(^{20}\).

The ratio of costs divided by effects is called the cost-effectiveness ratio. When two (or more) interventions are compared, the analyst will focus on the incremental cost-effectiveness. Therefore the cost difference between interventions is divided by the effect difference to obtain the incremental cost-effectiveness ratio (ICER) \(^{31}\).

While the relation to traditional welfare theory may have become unclear in CEA, the overall rationale remains maximisation of societal welfare. Adopting a perspective narrower than a societal one creates an additional problem. Which utility should be maximised by the health care production function, if not the societal? The budget constraint however relates to the health care budget and generally not beyond.
In CEA, the utility that is maximised stems from the health gain caused by the intervention. In other words, other utilities are disregarded. E.g. process utility being the utility gained (or lost) by patients or caregivers\textsuperscript{20,33,34} in the process of reaching the health state, is generally not considered.

The intuition of CEA is to achieve the maximum amount of health for a given budget\textsuperscript{35}, or alternatively to achieve the cost of reaching a desirable level of health. CEA is a tool for decision-making, as it provides a ranking of interventions according to the cost per effect. Effect measures in cost-effectiveness are outlined below.

**Effect measures**

Ideally, CBA should be used for economic evaluation because it maintains the theoretical rationale\textsuperscript{35}, cf. above. However the monetary expression of benefits in CBA is seldom feasible and therefore most economic evaluations in health care apply CEA, using QALYs or other non-monetary measures as the effect measure.

When CEA is used instead of CBA, the utility expressed by the benefit measure of CBA is expressed by a non-monetary measure. The effect measure either expresses final outcomes, such as quality-adjusted life years (QALYs)\textsuperscript{27}, gain in life years (LY) and healthy year equivalents; or intermediate outcomes such as a lower blood pressure (in e.g. the treatment of hypertension). The latter does not reflect health or health gain and should be translated into a final outcome in order to calculate the cost per health gain. The intuition behind this is that low blood pressure is not a goal in itself, while the improvement in health caused by the lower blood pressure is the actual goal of the intervention\textsuperscript{36}. Thus, an intervention that reduces blood pressure should be prioritised only because medical evidence suggests that a low blood pressure improves health, which is the true aim of the health care intervention. The cost-effectiveness analysis should therefore adopt a time horizon that allows for analysis of final outcomes such as QALY or LY.

For the final outcomes, the main difference between QALYs (and similar measures) and LYs, is that QALY, being a compound measure composed of a difference in LY and a change in health related quality of life (HRQoL)\textsuperscript{37,38}, is preference-based\textsuperscript{39}. The HRQoL instruments are used for describing different health states. Individuals’ preferences for these health states can be revealed through use of e.g. the standard gamble
In some studies, data on HRQoL are not available, as participants were not asked or could not complete the questionnaire due to their condition. Sometimes in the event that one lacks HRQoL data, data from other studies can be found in the literature or imputed\(^\text{41}\). Otherwise LY can be used as the effect measure.

**Costs**

While health outcomes in CEA are measured in terms of QALYs or other non-monetary measures, resource consequences of the analysed health care intervention are measured in monetary terms. Costs are identified as the change in resource use caused by the intervention, or, more precisely, the change in resource use from implementing the intervention compared to usual care\(^\text{42}\).

**Identifying costs**

The identification of costs in economic evaluation includes decisions on the perspective of costs and the time frame of the analysis, including the concept of survivor costs.

**Perspective of costs**

The aim of the economic evaluation is to inform decision makers of the comparative cost-effectiveness of a health care or health promotion intervention\(^\text{43}\); therefore the perspective of the analysis relates to the perspective of decision makers. Decision makers are based in different settings and therefore form decisions from their own perspective of responsibility\(^\text{44}\). Chapter IV identifies the following common perspectives in economic evaluation: the societal perspective, the health care sector perspective and the third party payer perspective. For an analysis of e.g. coronary angioplasty, an analysis from the health care sector perspective would comprise costs during admission and rehabilitation, as well as pharmaceuticals and use of general practitioners following discharge. A third party payer perspective would include health care costs and also costs in the social sector, such as home care or nursing homes. Examples of third party payers are the German ‘Krankenkassen’ and the American Medicaid or private health insurance companies. In Denmark, a third party payer would be the health care provider; which would have a similar perspective to the health care sector, unless the third party payer takes an interest in shifting costs from one public...
authority to another (e.g. from regions to municipalities). The main difference between the societal perspective on one side and the health care sector and third party payer perspectives on the other, is the inclusion of productivity and consumption changes, patient time costs, and economic effects on others, e.g. time spent by the patient’s family.

Most economic evaluations in health care apply the health care sector perspective or the third party payer perspective (this is elaborated in chapter IV). Inclusion of only health care related costs in the economic evaluation ignores the impact of the intervention in other sectors. Perspectives as narrow as the health care sector may render flawed results, as e.g. costs for the hospital department may not reflect true costs if costs are shifted to other departments, outpatient treatment or practising specialists. Most importantly, a single sector perspective may lead to a result that does not maximise the welfare of the whole society but only the welfare confined to that sector. This contradicts the welfare economics position that societal welfare should be maximised, cf. above. Further, a resource allocation that appears optimal within a single sector may be suboptimal or inefficient from the perspective of the entire society.

While the health care sector and the third party payer perspectives are not identical, they both maintain focus on health care related costs. The societal perspective presents a different approach than the health care sector related perspectives, but seems to be defined in various different ways. Some studies apply the societal perspective defined by the US Panel, in which income effects (consumption and production changes) are not considered beyond the so-called time costs; the time spent by patients in treatment. The recommendations of the US Panel are described below.

In addition to the impact on production and consumption, the societal perspective potentially comprises a number of other cost components: costs of informal care-giving, i.e. family members caring for an ill person; and costs of administrating social pensions and benefits for patients leaving the labour market due to the analysed condition. These cost components are seldom assessed, mainly due to important measurement difficulties.

While the definition of costs from a societal perspective seems somewhat ambiguous, this is also the case for health care costs, although to a lesser extent. Future unrelated health care costs are sometimes not included (this is elaborated in chapter IV). The distinction between related and unrelated health care costs
is unclear in many cases, rendering identification of unrelated health care costs difficult. Also, the precise
definition of the health care sector may differ between countries.

**Time horizon**

‘Ideally, the time horizon should be chosen in such a way that all cost consequences of the intervention
under study can be taken into account in the analysis’

Brouwer et al (2001), p. 71\(^{14}\).

In the design of a CEA study, decisions regarding the time frame of costs and effects are central. Both costs
and effects can occur immediately as well as in the long-term. For prevention, most costs and effects occur
at a later stage\(^{46}\). Also for health care interventions, relevant costs and effects can be identified several
years after the intervention.

The long-term of a health care intervention may be different from the short-term. An economic evaluation
of a health care intervention that covers a short time frame may not include all relevant costs and effects.
This was a crucial message resulting from the analysis in paper 3, which rendered different results when the
time horizon was expanded. To account for the insufficient information relating to the short time frame of
many studies, they often include a decision model (Markov model or similar), which extends the analysis
time horizon. In such cases the analysis time frame is expanded while the study time frame remains short.
In the case of the study time frame being too short, the model may render insufficient results.

The time frame of costs is as relevant as the time frame for effects and could, in fact, alter results
significantly. Lifetime costs depend strongly on length of life\(^{47}\). An intervention that increases life
expectancy causes health care costs and savings at higher ages, which may or may not be related to the
disease; e.g. a coronary angioplasty patient that lives long enough to suffer from cancer at a high age.

The nature of cost components is different in studies with relatively long time frames. In the cost
measurement, it may no longer make sense to distinguish between fixed and variable costs, as fixed costs
become variable\(^{14}\).

Compared with health care interventions, health promotion interventions will often have more important
cost consequences in the long-term than in the short-term. An intervention aiming to prevent alcohol
abuse will, if successful, decrease the incidence and mortality from alcohol-related diseases several years
after the intervention. Thus, there is a health care cost saving associated with the intervention, but only in
the long-term. The people that live longer and do not suffer from alcohol-related diseases will also at some stage need hospital treatment for other diseases, such as CHD. A moderate alcohol consumption is known to decrease the risk of CHD. Therefore, there may be other long-term health care costs associated with the health promotion intervention.

Consequently, if the analysis time frame of the health promotion intervention was short, e.g. one or five years, neither the cost figure nor the effect measure would be complete. The study period needs to be sufficient and can be combined with modelling. The same reservation applies to health care interventions that may incur related or unrelated health care costs as well as survivor costs at a later stage.

**Survivor costs**

Survivor costs, also called future costs, occur over a longer time perspective than the actual intervention. They comprise downstream health care costs, unrelated health care costs, production and consumption changes.

A long-term consequence of health care and health promotion interventions is a gain in LY, in most cases quality-adjusted, i.e. QALY. In added years of life, the individual that gains from the analysed health care or health promotion intervention may contribute to production and will, in any event, maintain a consumption of health care and non-health care goods and services. It is still being debated in the health economics literature whether these cost components should at all be included in the cost calculation. For interventions that improve health without having an impact on life expectancy, consumption and production could also change as a result of the improved health.

The magnitude of survivor costs can either be assessed in a long-term register-based or cohort analysis, or computed as the increased longevity known from the intervention, times an average figure for survivor costs generated from the background population, such as the costs computed in paper 4. Paper 4 also demonstrated that inclusion of survivor costs can alter the cost estimate considerably, underlining the importance of the perspective and time frame of the analysis.

**Cost measurement**

This section is concerned with issues relating to the actual quantification of costs, comprising top-down vs. bottom-up costing, including the concept of activity based costing.
Top-down vs. bottom-up costing

In top-down costing, the costs of e.g. a specific health care service are derived as the total costs of providing the service, divided by the number of patients using the service. The cost figures are usually based on accounting figures from the health service provider\textsuperscript{54}. Thus, top-down costing refers to estimation of average unit costs using available accounting figures. These unit costs are used for multiplication with the number of patients participating in the analysed health care intervention. Due to the use of accounting data, top-down data collection always takes place retrospectively\textsuperscript{44}. Costs in the health care sector are divided into fixed and variable costs, where the former category typically comprises buildings and large equipment and the latter comprises wages and other current costs, such as pharmaceuticals. The top-down approach often includes some elements of fixed costs, while this is not the case for bottom-up costing. In the short-term, fixed costs are often not included in the cost figure\textsuperscript{44}. For long-term analysis however, including fixed costs may be more appropriate, as the distinction between fixed and variable costs becomes unclear in the long-term\textsuperscript{14}.

Bottom-up costing is considered less feasible than top-down costing\textsuperscript{14}. The bottom-up costing approach follows a number of participants and records their resource use, arriving at a more precise figure for average costs and also obtaining figures for variance between patients. In addition, bottom-up cost figures can distinguish between costs for patients successfully completing the intervention and drop-outs. Health care costs unrelated to the intervention can be excluded if the perspective of the analysis prescribes it. Further, bottom-up costing can be carried out prospectively, if it is included in the design of e.g. a trial.

Most often CEA are based on top-down figures due to the feasibility\textsuperscript{14,44} and availability of cost figures or on a combination of top-down and bottom-up approaches\textsuperscript{54}. The latter, mixed approach, may however suffer from weak external validity due to incompatibility of top-down and bottom-up figures\textsuperscript{44}.

While bottom-up costing appears to be the most precise approach to cost measurement, it may render underestimated cost figures as some cost components could be ignored, including fixed costs in analyses of longer time perspectives.

Activity based costing

The activity-based costing approach was introduced as a link between health care services and costs, based on the notion that health care services \textit{per se} do not consume resources, but activities, and these employ
Valuation of costs

This section relates to valuation issues of the cost calculation in cost-effectiveness analysis, including the concepts of opportunity costs and unit costs, as well as discounting.

**Opportunity costs**

The costs in cost-effectiveness measurement are valued as the opportunity costs or the shadow price of the intervention\(^5\). In terms of Pareto efficiency, the opportunity cost is the net benefit foregone in order to obtain the health gain associated with the intervention\(^6\). Health care costs, being the time spent by health care personnel, use of pharmaceuticals and medical equipment, are valued by the best alternative use of resources, i.e. the opportunity cost of diverting resources from their best alternative use\(^7\).

Generally, costs represent a use of resources often valued by market prices or expenditures or accounting figures. In the ideal situation, cost information would be derived from the market equilibrium in which prices reflect opportunity costs. However in health care, prices may not reflect opportunity costs per se\(^8\) due to market distortions, or may even not be present\(^9\). The measurement of costs in cost-effectiveness analysis should overcome this challenge by adjusting market prices or using other proxies for opportunity costs\(^10\).

**Unit costs**

For measurement of the costs of a health care intervention, the analysis should identify relevant units required for the intervention (e.g. physician work hours), and a unit cost for these units. In market equilibrium, the wage of the health care professional equals the marginal benefit of their production. The unit cost is then the gross hourly wage paid to the employee. For other cost items unit costs should in principle be derived from market equilibrium prices if such exists. In effect prices of materials and resources\(^11\). Activities hence became a link between services and resources. E.g. a health care service such as a treatment of angina consists of several activities, including bypass surgery, anaesthesia, intensive care unit, nursing, x-rays, medication, etc. For each well-defined activity, the resource use is identified. Each discharge is then composed of activities, all with a well-defined resource usage. Activity-based cost figures represent a refinement of the bottom-up costing approach since it is based on the accounting principle of full absorption costing, i.e. both fixed and variable costs are included\(^12\).
equipment are valued at their market prices assuming that the se are sold in a perfect competitive market where the market price is equal to marginal production costs.

Unit costs can be derived either through bottom-up costing exercises\textsuperscript{54} or through top-down where cost figures are derived from expenditures, charges or tariffs, used under the appropriate assumptions\textsuperscript{14,44}.

**Discounting**

Costs in economic evaluations covering more than one year should be discounted to reflect that the time preference for costs in the future differs from costs in the present. A similar time preference applies to effects.

While there is no disagreement on the necessity of discounting, there has been some debate regarding the magnitude of the discount rate\textsuperscript{59}, including whether costs and effects should be discounted at the same rate\textsuperscript{60}. The US Panel recommends use of 3 percent p.a. as the discount rate for both costs and effects\textsuperscript{56}.

**Application of cost valuation**

The health care sector is characterised by market distortions, cf. above. For this reason, it is necessary to make some assumptions in the cost measurement and valuation. A common assumption is to use charges as proxies for unit costs\textsuperscript{44}. This occurs in the Danish primary health care sector and in countries with insurance based health care. However, charges may not equal costs, because they either exceed true costs, in the presence of profits, or are lower than true costs, when treatment is subsidised\textsuperscript{44}. Charges should only be used in the cost computation together with thorough knowledge of the relation between costs and charges\textsuperscript{61}. This issue is more central in countries such as the US where health care services are market based. For this reason cost-to-charge ratios have been developed in the US\textsuperscript{44}.

In the Danish health care sector, tariffs are widely applied. Hospital treatment is provided free of charge for the patient; however hospitals are budgeted according to their production, measured in DRG-points (diagnosis related groups). For each DRG, a tariff is calculated, based on average variable costs\textsuperscript{62}. The tariffs represent an attempt to create a market; however the tariffs apply universally and therefore ignore differences in the service provided and differences in opportunity costs between hospitals. Possible economies of scale are also disregarded as the same tariffs apply to the same treatment, regardless of hospital size.
In addition, cost figures based on tariffs are not completely correct because tariffs are used for remuneration in the health care sector, and could as such reflect the bargaining power of trade unions or employers rather than true resource use. In the Danish system, however, tariffs are used universally and are not subject to bargaining, therefore they can, under appropriate conditions, be considered reasonable proxies for true cost figures.

**Recommendations for CEA**

During the 1990s, a growing body of CEA put focus on the need for a common methodology and terminology in economic evaluation. As a response to this need, the so-called US Panel in 1996 issued a set of recommendations for economic evaluations of health care interventions. Since then, a number of countries issued their own guidelines for economic evaluation, often within the context of health technology assessment. The UK NICE guidelines are widely used and discussed also in other countries. The Danish and Swedish guidelines differ from the NICE recommendations in their recommended perspective, and from the US Panel in their interpretation of the societal perspective.

This section concentrates on the US Panel reference case for CEA. The reference case comprises, *inter alia*, the following elements:

- Costs and health effects should be assessed from the societal perspective.
- The impact of production changes on the individual should be captured by the HRQoL instruments used for the QALY estimation.
- Productivity effects on others, including friction costs, should be included, if significant.
- Time costs should be included, measured by wage rates.
- Resources should be valued by their opportunity cost, and assessed from a long-term perspective.
- Future health care costs and non-health care consumption should in theory be included, but this may not be possible.
- The time frame should be sufficient to capture all relevant costs and effects.
- Evidence for effectiveness may be obtained from a variety of data sources (RCTs, registers, other).

The US Panel argued that future income changes, as discussed above under survivor costs – or at least productivity gains for the individual – should not be included in the cost effectiveness measurement, as the benefit of the increased production is already accounted for. The explanation for this argument relates to the QALY calculation. The respondents replying to the time trade-off questions of EQ-5D or similar are
asked to imagine and subsequently value, a certain health state\textsuperscript{25,36,40}. In doing so, they may also consider the changes in productivity and consumption following from that health state, and take these into account in their valuation. Indeed the US Panel recommended that HRQoL was measured by an instrument that took future productivity changes into account. The US Panel found that if the utility arising from a productivity gain is part of the QALY, it should not be a part of the cost computation as well. Including the same item in numerator and denominator would be double counting\textsuperscript{45,56}.

The Panel did briefly consider the impact of productivity changes for individuals other than those gaining from the intervention. These should be included, if significant. In particular, friction costs should be incorporated if feasible. Friction costs cover the costs to employers when an employee leaves her position due to death or illness and a new person has to be recruited and trained\textsuperscript{66}.

For future health care and non-health care consumption, the US Panel argues that the most appropriate option is to include these future cost components, but due to feasibility considerations, one could choose to exclude them\textsuperscript{56}.

As argued above, the survivor costs of an intervention include costs to others and are not identical to the benefit for the individual. When the cost effect of surviving is divided into the impact on the individual and the impact on others, it appears that the latter is not included in the QALY, while it is debatable whether the impact on the individual is included in the QALY\textsuperscript{49,51,67-69}. Therefore for at least some of the survivor costs, inclusion in the numerator of the cost-effectiveness ratio would not be double counting. Instead, survivor costs form an integral part of the long-term cost, and should be included when the time frame of the study is long enough. In many cases though, data for this inclusion may not be available.

Aside from the excluded productivity costs, the US Panel argued for the adoption of a societal perspective, relating to the welfare theoretical rationale of economic evaluation. A narrower perspective could lead to inefficient resource allocations\textsuperscript{70}. The perspective of the economic evaluation appears to be the area where recommendations differ most. The NICE guidelines in the UK recommend application of the NHS perspective\textsuperscript{63}, hence leaving out costs and effects outside the health care sector. The Danish and Swedish guidelines recommend the societal perspective, while defining this somewhat broader than the US Panel, as they include productivity changes and other survivor costs\textsuperscript{64,65}.
The time frame of an economic evaluation should, according to the US Panel, be sufficient to capture all relevant costs and effects. Costs and effects occur at later stages; also the use of final outcomes (QALYs and LY’s) dictates a longer time frame.

While quoting hierarchies of evidence\textsuperscript{71} (such hierarchies are discussed in chapter III), the Panel was rather pragmatic in their approach to data sources and simply stated that evidence may be obtained from a variety of data sources, in their recommendation for economic evaluation.

**Cost-of-illness**

The so-called cost-of-illness (COI) studies measure health care costs and future costs of a given disease or disorder, but do not relate costs to effects\textsuperscript{17,46}. In a COI study, the costs of a given disease or risk factor is calculated, either on the basis of prevalence figures in burden of disease studies, or as costs per new case of the disease in question. The prevalence based COI is based on questions such as: How much does coronary heart disease cost the Danish society per year? On the other hand, incidence based COI results in a potential saving, if one case of coronary heart disease is avoided e.g. through successful prevention measures.

COI studies often apply a similar methodology for cost assessment as cost-effectiveness studies, but do not relate to a specific health care or health promotion intervention.

In the prevalence based form of COI, the average annual health care costs, social costs and productivity costs of the disease are calculated (and sometimes even assumed), and multiplied by the prevalence in a given year\textsuperscript{72}. As this approach disregards the differences between incident cases and people that have been living with the disease for ten years, the resulting figures cannot be used for expressing costs in CEA. The applicability of COI in decision making is rather limited because of COI not relating to effect measures. Therefore decisions based on COI results could lead to inefficient and suboptimal health care resource allocations\textsuperscript{73}. E.g. if decision makers are presented with a COI concluding that CHD is very costly, they could choose to spend resources on interventions that aimed to treat or prevent CHD but were not cost-effective.

A more refined COI analysis would, upon identifying people with the analysed condition, trace their health care costs and other cost components. Then, by identifying a comparable group of people without the
condition, calculate attributable costs as the average cost for people with the condition excluding average cost for people without the condition.

Even though the attributable cost method measures actual costs and thereby excludes costs that are irrelevant to the condition, the use of COI results still appears rather limited. A COI usually presents results as the annual costs to society of a given disease or condition. However, the condition may be preventable or curable if an intervention is timed appropriately. If, e.g., the COI result is the lifetime cost of a newly diagnosed case of CHD, it can be applied in an assessment of whether prevention of CHD is cost-effective. Paper 1 provides such cost figures\textsuperscript{16}. Or, if the COI assesses lifetime cost of new cases of myocardial infarction, it can be used for analysis of the cost-effectiveness of angioplasty.

An example of COI is shown in a recent study of obesity\textsuperscript{46}, which came to the result that, in a lifetime perspective, normal weight people incur more health care costs than obese people. Therefore, when aiming to minimise costs, obesity should not be prevented. The authors point out that the aim of health care was never only to reduce costs but also to increase health, and, from that perspective, there is still a case for preventing obesity. The main finding, which is reflected in the subtitle of the paper: ‘Prevention no cure for increasing health care costs’, relates to the finding of longer life expectancy amongst normal weight people than amongst obese and suggests that cost computations by themselves have little value as absolute measures\textsuperscript{46}. Since health care costs are related to age, the older people become, the higher their health care cost per life year, which is illustrated in paper 4.

Focusing on costs alone and comparing lifetime costs of obese people to those of normal weight people could lead to the strange conclusion that obesity incurs a societal gain. If, on the other hand, the costs of obesity were used in relation to the outcome of an obesity-preventative intervention, being a gain in LY or QALYs, this relative measure would provide decision makers with a tool for choosing between interventions.

Contrary to COI measures, the cost-effectiveness ratio provides decision makers with a tool for comparing interventions with each other, with usual care and with no intervention\textsuperscript{72/74}. COI can, if used correctly, be used for cost minimisation purposes, rooted in accounting rather than economic theory, or political organisations can use COI analyses for focusing public or political attention on a specific disease or condition.
Summary

In this chapter I have outlined the theoretical framework of CEA and some of its central issues. I have introduced the concepts and definitions of effectiveness and costs, as well as the US Panel Reference Case for CEA.

CEA is derived from CBA that rests firmly on welfare economics. This association prescribes that the most appropriate perspective for economic evaluations is the societal perspective.

In addition, it is of central importance that the economic evaluation covers a time frame that is sufficiently long enough to render results on final outcomes, preferably QALYs as they are preference based.

Finally, the rationale of CEA does not dictate use of a particular data source. Therefore, data sources used for economic evaluation do not need to be trial-based.

I now turn to an assessment of the data sources for costs and effects in CEA.
III. Evidence for economic evaluation

In clinical epidemiology, the main focus is the relation between exposure and outcome. In the case of health care interventions, that would be the relation between treatment regime and effect or efficacy, meaning the isolated effect difference between treatment regimes. The choice of data for these analyses traditionally follows a hierarchy of data sources in which the randomised controlled trial (RCT) is on top. This hierarchy originates from clinical epidemiology and exists in a number of versions\(^{71,75}\).

Meanwhile, the economic evaluation focuses on both costs and effects. In addition, measures of effectiveness, the real-world difference between treatment regimes, may be of higher value to the economic evaluation than measures of efficacy.

‘[f] our philosophical notion is that; (1) an economic evaluation is only as good as the data it is based upon, but (2) economic analysts must do the best they can with the available data. ’ [Authors’ emphasis] Drummond et al (1997), p 234\(^{20}\).

Issues other than adhering to a hierarchy may dictate the choice of data for economic evaluations, including applicability and validity. Drummond et al (1997)\(^{20}\) discuss the validity issue in their assessment of which data are applicable for economic evaluations. They state that the data from RCTs often have a high degree of internal validity while a restrictive protocol can impact negatively on the external validity.

Internal validity pertains to the strength of conclusions on efficacy or comparability of the analysed treatments. When the economic evaluation compares two treatments, its results should reflect differences between costs and effects of treatments and not differences between patient groups or other statistical noise. When the study has a high ratio of statistical signal to noise, it is said to have a high internal validity.

External validity relates to the applicability of results. If a trial finds that a particular treatment is superior to its alternative, physicians will tend to choose this treatment in their clinics. The external validity is directly associated with the trial results being replicable in an unselected population.
In this chapter, use of different data sources in economic evaluations is described and discussed, focusing in particular on validity and applicability.

The Randomised Controlled Trial

‘Randomized controlled trials (RCTs) are generally accepted as the most powerful tool for assessing the effectiveness of interventions, medications, or procedures.’
Mandelblatt et al 1996, p. 142

The randomised controlled trial (or randomised clinical trial: RCT) is defined as a comparative study of two (or more) treatments in a controlled setting. One treatment arm can be conventional care or placebo, however the presence of more than one treatment arm is a central feature of the RCT. Further, participants have to give informed consent before enrolling, they have to fulfil a certain set of eligibility criteria, and, most importantly they are randomised to treatment arms. Randomisation is considered necessary in order to avoid differences between treatment groups that could influence results.

The RCT sits at the very high end of the hierarchy of clinical evidence. A large, well designed RCT provides a high internal validity of results. This means that for patients in everyday clinical life that are identical to trial participants, the trial result provides information on the best treatment. Conclusions on efficacy or outcomes based on RCTs are used widely, also in economic evaluations, often with little recognition of the clinical applicability of results.

RCTs can be more or less restrictive and more or less protocol-driven. By a restrictive RCT is meant that the selection of patients for the trial is subject to a number of conditions. A very protocol-driven trial will tend to deviate from the everyday clinical setting to an extent that the external validity is potentially weakened. It is a common feature of trials that a certain age group is selected for the trial and that participants should be free of other diseases. Participants in a trial have to provide informed consent, which in some cases can contribute to selection bias.

The term selection bias refers to bias in the selection of individuals for a trial impacting on the findings. Selection bias can also occur in other types of studies, except for studies in a completely unselected population and where response or consent is not required. However for RCT the selection bias often relates to participants being ‘too healthy’ that is, more healthy than the average patient suffering from the...
investigated disease. Related to the issue of selection bias is attrition bias, arising when trial participants discontinue participation to a different degree in the treatment arm compared to the control arm.

In the event of selection or other bias, the results of the RCT will suffer from lack of external validity. Transferring results to clinical use becomes difficult, as the participants of the trial are not comparable with ‘normal’ patients. Clearly the usefulness of RCTs is limited when the external validity is poor. Drummond et al (1997) argues in favour of “pragmatic” trials, where the conditions are relaxed so as to increase the comparability with unselected patients in everyday clinical life.

Pragmatic trials are trials that are designed so as to resemble the ‘real world’ to a larger extent than ‘explanatory’ trials focusing on evidence for efficacy. This latter type of trial tends to create an ideal setting that is not easy to generalise to everyday clinical life. The pragmatic trials were introduced in order to reduce this perhaps most important weakness of RCTs. Pragmatic trials aim explicitly at applicability in real life settings, and report their results in order to assess applicability. Therefore, the main difference between pragmatic trials and explanatory trials is the inclusion criteria. The pragmatic trial maintains randomisation but does, due to the relaxed inclusion criteria, present a more heterogeneous study population. The Beich et al (2007) study provides an example of pragmatic trials. They focused on an intervention aimed at preventing alcohol abuse. Inclusion criteria were rather relaxed and masking or blinding was not feasible due to the study set-up in general practice.

The difference has been explained as explanatory trials focusing on efficacy and pragmatic trials on effectiveness. Others have argued that, in the event of a pragmatic trial finding no effect, it is difficult to establish whether the reason for this is the design of the trial or if there would have been no effect in an explanatory setting. This argument applies to significant findings too and relates to the potentially weaker internal validity of pragmatic trials.

The internal validity is probably even weaker in cluster-randomised trials. A cluster-RCT is a trial, in which intact groups of eligible patients are randomised to different treatment arms, as opposed to the standard RCT where individual patients are randomised. The groups or clusters are often defined as organisational units, such as hospitals or GP practices. As such, the cluster-RCT may be more similar to a register-based study, where differences in patient characteristics need to be adjusted for.
When RCTs are given first priority in the assessment of effects, internal validity is prioritised over external validity or, in other words, efficacy is prioritised over effectiveness. Since the economic evaluation concentrates on cost-effectiveness, cf. chapter II, the rationale of a hierarchy that prioritises efficacy over effectiveness is not clear.

If costing is included in the design of a RCT, it is possible to carry out a prospective, and potentially bottom-up cost assessment, which can be more detailed compared to a retrospective cost computation. Often however, the RCT-based cost assessment is based on top-down assessments, accounting figures or ‘piggy-backed’ cost collections, neither of which are superior to a register-based cost computation. Using cost assessment alongside RCTs (piggy-back) may generate results that deviate from a real-world situation. If trial patients are ‘too healthy’, their health care costs consequently are ‘too small’. On the other hand, the cost of the trial set-up, and the cost of the redundant trial resources if too few patients fulfil participation criteria or agree to participate, could inflate cost figures. In the case of redundant trial resources, the analysis may be based on the assumption of efficient use of resources and not observations of real costs, rendering cost conclusions uncertain. Further, trials are often conducted in large university hospitals, where the cost structure may be different from smaller hospitals.

Other issues that potentially render the RCT imperfect for use in economic evaluation comprise the choice of ‘usual care’ and a sample size that could cause statistical power problems.

External validity has retained focus as the most important problem with RCTs; and can be solved e.g. through use of pragmatic trials. Another problem has not been discussed as thoroughly. Since trials are often conducted within a short time frame, long-term effects (and costs) are disregarded. Effects can be divided into intermediate and final outcomes; intermediate outcomes are e.g. readmissions within 6 months or a year, while the final outcome typically is mortality. Due to the limited time frame of the RCT, the focus remains on the short-term outcomes. There are no features of the RCT that prevent long-term analysis; however there may be a pressure from decision makers, pharmaceutical companies and others, for the trial to render results. Therefore funding for the trial may only be obtainable for short time periods. Due to these time restrictions and perhaps also statistical power problems, as trial populations are often small, many trials focus on intermediate outcomes. The analysis time frame is sometimes extended beyond the short study time frame in order to assess final outcomes. To this end modelling or extrapolation is used. This is described later in this chapter.
Since long-term consequences are important for both health care and health promotion interventions\textsuperscript{43}, the short analysis time frame of many RCTs is potentially a problem.

There remains a wide scope for use of RCT-based evidence, however in many cases this evidence is not superior to other types of evidence, either due to RCTs being small and restrictive, or in the presence of good quality register-based data\textsuperscript{71,87}. Thus, for economic evaluations, choosing RCT-data based on a hierarchy may not always be the optimal strategy.

Register-based data

The term ‘register-based data’ covers a variety of data sources, including cohort studies, research registers, clinical databases, administrative registers and accounting databases. Most often individuals are selected for inclusion in the register on the basis of their residence, condition, treatment hospital or similar. Registers that are designed for research purposes, such as cohorts, contain a number of variables that potentially could confound results. Hence cohorts are designed so as to account for some central weaknesses of registers and therefore often provide quite powerful data sources for research.

Administrative registers are perhaps in the opposite end of the spectrum as they are designed with a different purpose and may not contain the information sufficient to adjust for all confounders, nor for collection of all relevant cost data\textsuperscript{44}. In between cohorts and administrative registers are data sources such as patient registers and clinical databases. For use in cost-effectiveness analysis, registers should ideally contain both information on the disease and the costs involved\textsuperscript{43}.

Validity

Studies of health care or health promotion interventions based on register-data are regarded as inferior to RCT-based studies mainly for reasons of internal validity. A register-based study typically compares the effect of a new treatment or intervention offered to one patient group, with the effect of standard treatment offered to another patient group. In some studies, standard treatment is offered up to a specific point in time, after which the treatment regime changes, and the new treatment is offered universally. Thus the register-based study compares the patient group at one point in time to a comparable group at another point in time (e.g. one year later). Other register-based studies compare the group of patients in one hospital to a group of patients in another hospital, while yet other studies compare two or more
different patient groups in one clinic. A common feature for all types of register-based studies is that patient groups may not be entirely comparable.

Those register-based studies that compare treatments at different points in time may suffer from a weak comparability of treatments, as everything else may not be equal between the two points in time. Also, it should be considered that patient characteristics may change when the treatment regime changes. E.g., a new supposedly superior treatment is offered to patients for whom the standard treatment was considered unfeasible.

Similarly, patient characteristics could differ between two hospitals taking part in a register-based study. When the two patient groups are treated alongside each other in one clinic, the indications between treatments may be different.

Thus, compared to RCTs, analyses based on register data contain more noise and therefore the internal validity is potentially weak. On the other hand, external validity appears to be quite good in register-based studies, as results can be more easily generalised, and hence applicable in real-world settings. For register-based studies, it should be carefully considered if all or most possible confounders can be adjusted for. Most register-based data contain information on age, gender, socio-economic status and other features that can be used for adjustment. Adjustment is necessary in order to isolate treatment effect from the effect of covariates. In cohorts, or register data merged with survey data, information such as HRQoL and self-reported lifestyle is often recorded. However if such items are not recorded in the register, potential differences between patient groups cannot be adjusted for. Co-morbidity constitutes a related problem. If the patients receiving one treatment are more ill (e.g. they may have a higher prevalence of diabetes) than the patients receiving the other treatment, this difference could flaw the analysis and ultimately the results. Some registers comprise information on treatment for other diseases and hence co-morbidity, allowing for appropriate adjustment. For methods of adjustment, see below.

Findings on effectiveness are also easier generalised in the register-based study than in the RCT, although some reservations may apply. E.g., if one hospital is applying the new treatment and another is applying usual care, results from one hospital may not apply universally to the other hospital, as there may be demographic differences between hospitals or differences in level of expertise or other differences that possibly affect the treatment outcome.
For cost measurement, register-based analysis may in fact be superior to RCTs. A register-based cost assessment can relatively easy be generalised to everyday clinical life, as the reservations for generalising of the RCT do not apply\textsuperscript{90}. The applicability of register-based data renders these data more valid for evaluation of cost-effectiveness in real-world settings, than data from RCTs that do not resemble the real world to the same extent.

**Time frame**
A strong advantage of retrospective register-based studies is that they, more often than RCTs, allow for analysis of long-term consequences as a current outcome of an exposure in the past\textsuperscript{88}. In addition, duration analysis of survival or labour market affiliation can be conducted over long periods of time. In paper 2, we conducted a duration analysis of labour market affiliation amongst CHD patients for up to 23 years based on register data\textsuperscript{13}.

For analysis of most health promotion interventions, the relatively long time span between the intervention and the final outcome provides an additional challenge. E.g. the final outcome of a smoking cessation programme will only materialise much later in life, when the participants live longer and experience less disease. Therefore, economic evaluation of health promotion programmes requires either a register with long follow-up time or simulation of the long-term effects. Paper 1 provides an example of a cohort study where the impact of lifestyle interventions are analysed\textsuperscript{16}. For health care interventions as well, the longer time horizon of register-based studies allows for analysis of final outcomes as opposed to intermediate outcomes. The time horizon of costs is very important as well. As demonstrated in paper 3, expanding the time frame can alter results due to the inclusion of longer-term costs in the analysis. These long-term costs are often more readily available in register-based studies, in particular retrospective studies, than in RCT studies.

**The efficacy-applicability trade-off**
Whether register-based data are in fact inferior to RCT data, as suggested by various hierarchies\textsuperscript{71}, depends on the relative importance of external versus internal validity, or applicability versus efficacy\textsuperscript{79,82}. The applicability-efficacy trade-off is central for the choice of data sources in economic evaluation. While it can be argued that RCTs are necessary in the process of establishing the efficacy of an intervention\textsuperscript{82}, applicability may be much more important when assessing cost-effectiveness. Economic evaluations are usually used to make decisions on whether to implement interventions in real clinical life, and therefore applicability of analysis results is very central. In studies where the effect difference between interventions
is negligible, there is still a rationale for CEA. In the event of an intervention displaying a significant effect in a RCT, but having null effect in a register study, decision makers should take into account that application in real life could produce a null effect as well.

In Denmark, there exists a variety of registers that can be applied for CEA. In papers 1 and 2, we used the DANCOS cohort, comprised of national health interview survey data merged with comprehensive register data on health care utilisation, labour market behaviour, socio-demographic characteristics etc., allowing for analyses that include both self-reported health and lifestyle and register-based information. The ability to adjust for almost all possible confounders renders this cohort a powerful data source for analysis of costs and effects. In paper 3 we applied a patient register with detailed clinical information but also including register-based demographic characteristics and self-reported lifestyle parameters. These data sources provided information of sufficient magnitude and quality for the performed analyses. Paper 3 is an economic evaluation of two interventions used in real clinical life. We were able to adjust for several confounders in order to take into account that the two patient groups had different characteristics at baseline.

In summary, the choice of data for economic evaluations should be based on the efficacy-applicability trade-off rather than a hierarchy, as register-based data in some cases may be superior to RCT data, namely in those cases where applicability is considered more important than making conclusions on efficacy.

**Using register-based studies in economic evaluations**

Analysis of register-based data can take place as either time series, cross-sectional or as panel data analysis. Time series analysis focus on the development of indicators over time, while a cross-sectional analysis focus on the differences between individuals at a certain point in time. Panel data analysis combines the two and analyses differences between individuals and between periods simultaneously. A panel data set will usually contain a number of variables per individual in more than one period of time. A cohort constitutes a good example of panel data; indeed most register-based analysis in the field of health care takes the form of panel data analysis. While one-period cross-sectional data could be applied in economic evaluations, time series data are of rather limited relevance in this field.

The cross-sectional or panel data include a number of variables on health care utilisation that are useful for cost assessments. E.g. hospital admissions coded with the relevant DRG-tariff, or specialist services coded
with applicable charges. Further, the data comprise variables that can be used for effect measurement, such as health status, HRQoL and mortality. And finally, the panel data contain variables that are possible confounders and should be used in adjustment for confounders. Examples of such variables are age, gender, socio-economic variables, lifestyle, and residence.

As described in chapter II, the economic evaluation compares costs and effects of two or more treatment regimes. In the register-based economic evaluation, patients or participants are divided into groups according to their treatment regime. The analysis identifies cost differences and effect differences between groups, adjusting for appropriate covariates.

The register-based analysis is often a regression analysis. In the linear (ordinary least squares) regression model, costs or effects are expressed as a function of treatment group and appropriate covariates. The model includes an error term and is subject to a number of assumptions. Firstly, the relation between dependent and independent variables should be linear, and secondly the error term is subject to a number of restrictions, e.g. it should be normally distributed and must not display heteroskedasticity (when error terms have different variances). For cost data in particular, the assumption of normally distributed error terms is often violated. In order to apply the linear regression model, data are prepared by means of logistic transformation. Results are retransformed by means of smearing techniques. The advantage of the linear regression model in economic evaluation is that the group or treatment regime parameter presents a quantification of the cost or effect difference between groups. In paper 1 we applied linear regression with logistic transformation for computing the health care costs of heart disease and risk behaviour.

Other regression methods comprise logistic regression and generalised linear modelling. For survival or duration analysis, such as the one performed in paper 2, Cox regression is most often used. The result of the Cox regression is a hazard ratio, expressing the difference in risks of a certain outcome between groups. The Cox regression assumes proportional hazards, meaning that the relationship between the risks of the compared groups should be constant over time. If this assumption is violated, other models should be applied. In paper 3, the proportionality assumption was violated and a Weibull accelerated failure time model was therefore used to identify the effect difference between groups.

A key issue in the register-based economic evaluation is the adjustment for relevant covariates. In this process, firstly possible confounders need to be identified. A number of covariates, such as age, gender and
socio-economic parameters, are almost always included in the analysis. For other variables, a non-parametric test can verify whether there is a detectable and significant difference between groups. Most often, the impact on results of potential confounding variables is tested by including and excluding these variables in the model.

When the number of covariates that potentially qualify for adjustment is high, the effect of each covariate becomes difficult to identify in the regression model as the explanatory power becomes insufficient. A solution to this problem is to summarise information on all relevant covariates in the propensity score\textsuperscript{94,95} which is a compound measure consisting of all covariates, generally transformed into a scalar and grouped into quintiles. The regression model becomes quite simple as the explanatory variables are reduced to two: treatment group assignment and propensity score quintile.

Thus, register data in the form of panel data and cross-sectional data provide a strong basis for economic evaluation as they contain not only a variety of applicable analysis variables but also vast opportunities of adjustment for those covariates that could potentially bias results.

**Meta-analysis and decision modelling**

Meta-analyses and decision models represent ways of analysing costs and effects of health care interventions in the absence of applicable RCT or register data for the desirable time frame. The meta-analysis usually compiles RCTs within a given area and draw conclusions based on the compiled data. The trials put together represent a larger analysis population and lesser uncertainty.

Decision models can acquire their data from RCTs or register analyses or both. The model is built around these data while assumptions about mortality and similar features are based on population data. They often take the form of a Markov model, in which patients either remain in a given health state, or move into another health state. Health states can be, e.g., disease-free, recurring disease, or dead. The probabilities of moving from one state to another, the transition probabilities, are based on data from RCTs or registers. The Markov model can simulate any number of years; often a cohort is followed for lifetime. RCTs will normally not provide sufficient data for the long-term analysis, as their time frame is much shorter. For the analysis of lifetime effects, assumptions are made regarding the changes in transition probabilities over time. E.g., when a CHD patient has a stent implantation during angioplasty, little is known of the long-term effects of the implantation or the health care costs over a longer period of time.
For analysis of costs over the longer term, decision models also derive their transition probabilities from available data or from the literature. Costs relate to the health states described by the Markov model. It is assumed that the cost of a repeat surgery is the same regardless whether it takes place six months or six years after the index surgery. Unrelated health care costs may however change over time, in most simulation studies these are derived from the literature.

As meta-analyses and simulation models are based on existing RCT and register-based data, problems of internal and external validity, statistical power problems and similar are inherited from the original data. Observations regarding strengths and weaknesses of RCTs and register-data thus also apply to their secondary use. A good meta-analysis is, however, in some hierarchies of evidence considered superior to the RCT, as the compilation of RCT data accounts for some of the problems associated with single RCTs.\textsuperscript{71}

However, use of decision models can extend the time frame of the economic evaluation from the short to the long term, thus accounting for the reservation that most RCTs, and some other studies, apply a time frame that is too short to capture all relevant costs and effects. The uncertainty relating to the development of costs and effects beyond the trial period should however be analysed\textsuperscript{43}.

**Summary**

In this chapter, I have assessed three categories of data for economic evaluations: RCTs, register-data and meta-analysis or decision models. I have argued that register-based data may be of greater value than trial data in the assessment of costs, and that the prioritisation of data for effect measurement depends on one’s position on the efficacy-applicability trade-off rather than on a hierarchy.

When analysing costs and effects within a sufficient time frame, register-based data may be more appropriate than RCTs due to a longer time horizon of costs. Use of decision modelling can expand the analysis time horizon thus enabling the analysis to capture all relevant costs and effects.
IV. Literature review

As outlined in chapter III, data for economic evaluations originates from different sources: notably RCTs and register-based data. Also, the approach, perspective and time frame of the economic evaluation differ between studies. While there are some attempts at establishing a reference case for economic evaluations, notably by the US Panel\textsuperscript{45-56} but also by some national agencies in Europe\textsuperscript{63-65}, these have not been followed universally. In this chapter, I assess register-based, RCT-based and model-based economic evaluations in recent literature on CHD, focusing on their perspective and time frame and the data sources applied in the analyses. Finally I will relate the findings of the review to selected items of the US Panel reference case.

The review was limited to health care interventions aimed at CHD, and the focus of the review was firstly the perspective stated by the evaluation study, being societal, health care sector or other, secondly, the time frame of the study, and, finally, the methods used for gathering data for the evaluation, being RCT, register-based data, or modelling of RCT-data or register-data.

Search strategy

The databases Pubmed, Cochrane, the HTA database and the NHS economic evaluation database were searched for combinations of the following terms: ‘cost-effectiveness’ or ‘cost-utility’ in combination with ‘coronary heart disease’ or ‘ischemic heart disease’ or ‘angina’. Studies had to be published from January 2005 to March 2009 and had to be in English. Further, only studies with explicit and replicable cost estimates were included; and the analysis should relate to interventions that directly involved patients. In other words, economic evaluations of laboratory techniques or organisational changes were excluded.

Figure 1 displays the search process and the definition of eligible studies.
Figure 1: Overview of inclusion procedure

From the initial search, 149 studies were identified. Out of these, 61 fulfilled the eligibility criteria. 23 were based on RCTs, 9 on register-based data, 18 studies were decision modelling studies which were based on RCTs (n=8), on register-based data (n=5) or on meta-analyses which could comprise both RCT and register-data (n=7). The remainder were meta-analyses based on RCTs (n=5) and on register-data and RCTs (n=4).

Meta-analyses and decision modelling studies were categorised according to the type of data they were based on. Therefore, the 61 studies were categorised as follows: RCTs, register studies and studies based on combined data sources. Each category was subdivided according to use of a decision model (Markov model or similar) or not. The 61 eligible studies are displayed in table 1:
Table 1: Cost-effectiveness studies of coronary heart disease interventions – categories and cost perspectives

<table>
<thead>
<tr>
<th>Study type and references</th>
<th>Number of studies</th>
<th>Health care sector perspective</th>
<th>Third party payer perspective</th>
<th>Societal perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials 96-131</td>
<td>36</td>
<td>29</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Register based studies 132-145</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Studies using a combination of register and RCT 146-156</td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>44</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

Perspective

In this review, studies were categorised according to their own perception of perspective. Perspectives were divided into the health care sector perspective, e.g. the NHS in UK studies 63, the third party payer perspective (e.g. a German ‘Krankenkasse’ or an American insurance company) and the societal perspective. The latter appears to be defined differently in different studies.

As described in chapter II, the US Panel argued that the cost computation of an economic evaluation should apply a societal perspective on costs 45;56. From Table 1 it appears that application of a societal perspective was stated in 7 of the 61 reviewed studies. Amongst the seven studies, there appears to be some discrepancy regarding the definition of the societal perspective. In some studies the societal costs were identical to health care costs 103;109;147, one study regarded the societal perspective to be health care costs plus patient time costs 98 while three studies included productivity costs and to some extent also net consumption in added life years to their cost estimate 101;146;153.

These three studies, all Swedish, mentioned the Swedish guidelines for economic evaluations in health technology assessment and its recommendations to include also ‘indirect costs’. The Berg et al paper 153 analysed the cost-effectiveness of Clopidogrel (a pharmaceutical) in the treatment of myocardial infarction, using a decision model based on RCT data from three countries: Sweden, France and Germany. As the Swedish guidelines differ from the French and German guidelines, total costs were computed differently for the three countries. Therefore, the broad societal perspective was only applied for the Swedish data. Berg et al stated that indirect costs comprise productivity costs only. They reported the direct costs of
myocardial infarction in Sweden to be €5,700 and indirect costs more than €12,000, or more than double the direct costs. With a reference to Meltzer (1997)\textsuperscript{53}, they also included survivor costs in a sensitivity analysis. The result of this analysis was not reported, although it was mentioned in the text that including survivor costs would entail a cost saving for patients aged less than 64 and additional costs for older patients.

The Lindgren \textit{et al} (2005) study also pertained to Clopidogrel treatment, here in combination with aspirin and aimed at angioplasty patients\textsuperscript{146}. The cost assessment of this study also applied a societal perspective. As for the Berg \textit{et al} study, indirect (productivity) costs were included (and excluded) in a sensitivity analysis, and survivor costs were included in another sensitivity analysis. When survivor costs were included, the ICER increased almost threefold. Contrary to the Berg \textit{et al} study, Lindgren \textit{et al} found indirect cost of a much smaller magnitude, 10-20 percent of direct medical costs. It seems that there is a discrepancy between the findings in these two studies with regard to the magnitude of indirect costs. As the analysed treatments of the studies were rather similar and there were no major age differences between patient populations, this difference must be related to computation methods.

Lindgren \textit{et al} (2007) focused on the cost-effectiveness of statin treatment in the secondary prevention of coronary heart disease. More specifically, they compared high-dose Atorvastatin with regular dose Simvastatin in four Scandinavian countries. The study applied trial data in a lifetime Markov model\textsuperscript{101}. The authors included ‘indirect costs’ or work absence, and estimated the value of indirect costs as equal to the average wage plus the employer’s contribution. The latter component was not specified but may be interpreted as profit. Including a profit term implicitly assumes that the analysed labour market is not in equilibrium; however the inclusion of the profit term was not discussed in the study. The total indirect costs amounted to about €1,150 per week of work lost in Denmark and less than half of that amount in Finland. As the study analysed a secondary prevention intervention, there was a productivity gain related to the intervention, and therefore the total costs were reduced as a result of including productivity costs, more so in Denmark than in Finland.

Although the same first author in a previous study\textsuperscript{146} estimated survivor costs of the analysed intervention, this option was not included in this study, and the societal perspective was limited to inclusion of productivity gains.
The societal perspective was stated in four other studies. Chan et al (2007) made a reference to the US Panel in their approach to cost calculation, however only direct medical costs appeared from their overview of cost components\textsuperscript{109}. Similarly, Schleinitz and Heidenreich (2005), in their assessment of different combinations of pharmaceuticals in the treatment of myocardial infarction\textsuperscript{103}, as well as Mahoney et al (2005) in their analysis of Clopidogrel\textsuperscript{147}, stated the societal view but seemingly did not include cost components outside the health care sector. Hence, for these studies the societal perspective was equal to the health care sector perspective.

Hay and Sterling (2005) seems to be the only reviewed study to have adopted the recommended perspective of the US Panel reference case, as their cost figure included patient time costs spent in treatment\textsuperscript{98}. They also compared their finding to the societal threshold of costs per QALY. Hay and Sterling analysed the cost-effectiveness of a preventive measure, treatment of low HDL-cholesterol, as a primary prevention of coronary heart disease.

Prevention of a potentially fatal, serious disease such as coronary heart disease is likely to render a significant gain in life years and therefore also incurs important changes in productivity. According to the US Panel, these changes are included in the QALY\textsuperscript{45;56}, however this does not apply to the resulting opportunity costs for others. Primary prevention of coronary heart disease through cholesterol management is an example of an intervention where inclusion of survivor costs would have had a major impact on results.

The majority of the reviewed studies were confined to the health care sector, and sometimes even narrower, regarding only drug costs\textsuperscript{110;138} or programme costs\textsuperscript{123;137}. The study by Finkelstein and colleagues (2006) analysed a lifestyle intervention aimed at preventing coronary heart disease\textsuperscript{137}. Therefore, their choice of applying a programme perspective is not obvious. Large cost savings, in the health care sector as well as for society as a whole, could be obtained through a successful prevention measure. Including only programme costs renders the prevention programme less cost-effective than would have been the case, had the authors applied a broader cost perspective.

Most studies that applied the health care sector perspective included future unrelated health care costs, although only for the study period\textsuperscript{105;106;118-120}. British studies such as Campbell et al (2005) and Briggs et al (2007) applied the perspective of the NHS, which includes also unrelated health care costs\textsuperscript{107;108}. This,
however, was not always the case. A few studies stated the health care sector perspective but did not include unrelated medical costs\textsuperscript{116,155}.

Economic evaluations of health care interventions with a limited time frame did not consider health care costs beyond the specified time frame. The time frame of studies is also important for the findings of the economic evaluation.

**Time frame of studies**

Data collection in an economic evaluation takes place within the study time frame. Application of a decision model extrapolates the findings of the study period and thus expands the analysis time frame beyond the study time frame. The focus here is the analysis time frame. A reservation should be made; however, regarding extrapolation of findings from a very short study time frame. As described in chapter II, the US Panel recommended that an economic evaluation applied a time frame being sufficient to capture all relevant costs and effects\textsuperscript{45}. This recommendation relates to the analysis time frame, while the study time frame should be sufficient as to render results to be used for the extrapolation. In studies without extrapolation, the analysis time frame is identical to the study time frame.

For chronic diseases a sufficient time frame is several years or lifetime. Of the 61 reviewed studies, about a third applied the lifetime perspective on costs and effects. Decision model studies were well represented in this category. The extrapolation in the decision model allows for assumptions beyond a RCT or register time frame. In particular for RCTs with the popular time horizon of one year or less, extrapolation provides a means of analysing the long-term perspective. Almost half of the reviewed studies are RCTs without extrapolation. Compared to the other half of the reviewed studies they had a rather short time horizon. 75 percent of RCTs without extrapolation had a time frame of less than five years. In table 2 the studies are divided according to analysis time frame, type of data source and whether findings had been extrapolated or not.
Table 2: Analysis time frame of economic evaluation studies

<table>
<thead>
<tr>
<th>Study type and references</th>
<th>Less than a year</th>
<th>1 year</th>
<th>More than 1 year and less than 5 years</th>
<th>5-50 years</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapolation\textsuperscript{96-105} (N=8)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>No extrapolation\textsuperscript{104-131} (N=28)</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Register based studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapolation\textsuperscript{132-138} (N=5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No extrapolation\textsuperscript{137-145} (N=9)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Studies using a combination of register and RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapolation\textsuperscript{146-152} (N=7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>No extrapolation\textsuperscript{153-156} (N=4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total all studies</td>
<td>4 (7%)</td>
<td>11 (18%)</td>
<td>11 (18%)</td>
<td>14 (23%)</td>
<td>21 (34%)</td>
</tr>
</tbody>
</table>

Only a few studies applied the limited time frame of less than a year\textsuperscript{112;118;131;138}. The study by Zebis \textit{et al} (2008) analysed the cost-effectiveness of Amiodarone, a pharmaceutical given to coronary bypass patients immediately after surgery in order to prevent atrial fibrillation as a post-operative complication\textsuperscript{131}. The effect measure was cases of atrial fibrillation avoided, and since this only occurs during admission, the authors chose to include only costs during admission. Thus, the authors ignored not only downstream health care costs but also the impact on survival and HRQoL of avoided atrial fibrillation during admission.

The study by Fischell \textit{et al} (2006) focused on the use of Eptifibatide – a pharmaceutical that prevents complications following angioplasty\textsuperscript{138}. The authors chose a time frame of one month, thus disregarding downstream health care cost savings beyond one month, and potential QALY effects of avoided complications.

Lewin \textit{et al} (2009) analysed the cost-effectiveness of a rehabilitation scheme for patients receiving an ICD, and included physical and mental health as well as hospital admissions as effect measures\textsuperscript{118}. An ICD is implanted for more than six months and it is therefore somewhat surprising that the authors have chosen the short time frame of six months for their assessment.
Several studies applied the time frame of one year\textsuperscript{106;108;110;116;121;122;127;128;137;142}. Many RCT studies used the trial period as the study period for costs and effects and failed to discuss the possibility of future costs (including downstream medical costs) or effects occurring beyond the trial period. However, also some register based studies applied a limited time frame. The Finkelstein et al study\textsuperscript{137}, which was also discussed above, was a register-based analysis of a prevention programme, which seemingly disregarded effects and costs, including savings, in other sectors as well as in the longer term. It appears that the particular prevention programme did not receive a fair treatment. Effects of a prevention programme, including health care costs savings (as well as savings in other sectors), could easily materialize several years from the intervention.

Illustrative of the problems relating to the short time frame are the findings by Briffa et al (2005)\textsuperscript{106} in their evaluation of a cardiac rehabilitation programme, which constitutes secondary prevention and therefore is likely to have an impact on the longer term. The study was based on a trial and analysed costs and effects for one year. The authors found an ICER of 42,535 Australian dollars (approximately €25,000) for cardiac rehabilitation compared to conventional care. In a sensitivity analysis, the time frame was extended to three years, which rendered an ICER of 27,030 Australian dollars (€16,000). This finding underlines the significance of the selected time frame.

The Ohsfeldt et al (2006) study focused on statin treatment in primary practice\textsuperscript{142} but only followed patients for one year. As statins are used for prevention of coronary heart disease, the reservation regarding time frame of analysis of prevention programmes applies to this study as well. An example of a cost-effectiveness study of a prevention measure which applies a lifetime horizon is Quist-Paulsen et al (2006)\textsuperscript{123} that assessed smoking cessation programmes as a means of preventing coronary heart disease. The full impact of smoking cessation on costs and effects was seen in the lifetime perspective only.

To summarise, health care interventions can have long-term consequences as well as future costs or cost savings that are disregarded in economic evaluations with a too short time frame. Studies focusing on intermediate outcomes such as the prevention of post-operative complications\textsuperscript{131;138}, ignore the impact of the intermediate outcome on final outcomes such as QALYs. On the contrary, preventive measures usually incur costs on the short-term and costs and savings on the longer term. Also, the effect of a prevention measure is rarely limited to the short-term. Therefore, when analysing both prevention measures and
health care interventions in general, the time frame as well as the perspective should be chosen carefully, taking all possible costs and effects into consideration.

Data sources

The economic evaluation needs to be based on some data on costs and effects of interventions. These data could be drawn from RCTs or registers, and findings could be extrapolated in order to expand the analysis time frame. The US Panel drew no strong conclusion on the desirability of RCTs versus register-based data in their described reference case\(^41\). Both data sources for economic evaluation have advantages and disadvantages as discussed in chapter III.

Here, the data sources for economic evaluation were grouped into three categories, crudely disregarding the vast differences within each category. For RCTs, some are small and include patients that may not be representative of the relevant patient population\(^{106;108;112;114}\), while others are meta-analyses\(^{104;105;109;115;117}\) or piggy-backed on large trials\(^{107;110;111;113;116;119;121}\). It is not possible to draw any conclusions about external validity overall for this category.

In addition to the external validity of effects, cost-effectiveness studies based on trial data may not reflect the costs that could occur in a real, clinical setting. Indeed, this issue was addressed by Lindgren et al (2007) in a trial-based cost-effectiveness analysis of statins in secondary prevention:

‘As we used trial data to estimate the cost associated with each MI and revascularization, it is possible that some potentially important cost-drivers has been omitted.’

Lindgren et al (2007), p. 1451\(^{101}\)

An example of this omission is discharge to nursing homes, which is rather costly. If trial participants were healthier and hence less costly than patients in the real world, the cost-effectiveness results could change markedly if based on real world data.

Similarly, register-based studies assessed the internal validity challenge very differently. Most register studies were major cohorts\(^{137;139;141;143-145}\), and thus comprised a number of variables for adjustment, while at least one study was perhaps too small to comprise sufficient information on possible confounders\(^{138}\).

The study by Ohfeldt and colleagues (2006)\(^{142}\) represented an example of a register-based study which involved a major effort to deal with the issue of internal validity. The authors have analysed the
effectiveness and cost-effectiveness of different statins for prevention of coronary heart disease in routine clinical practice. They selected a cohort of patients by a set of eligibility criteria and adjusted results for several parameters collected at entry. When parameters from a comprehensive list of possible confounders are collected and subsequently adjusted for, the presence of another confounder that would markedly change results if adjusted for, becomes highly unlikely.

The validity discussion seems to have concentrated on internal and external validity of effects, while the validity of costs has been disregarded to some extent. In the register-based studies, where cost information was derived from the register or from administrative data from the ‘real world’, cost figures will normally reflect or be close to the true costs of the intervention and its consequences. As mentioned by Lindgren et al (2007)\textsuperscript{101}, this may not be the case for RCT-based cost computations.

To summarise, the issue of external validity is handled best by studies based on observational data, registers or cohorts recruited from the ‘real clinical world’. The challenge of these studies relates to the internal validity, or the minimisation of statistical noise. Most of the register-based studies reviewed here approach this issue carefully by accounting for a comprehensive set of possible confounders.

Is there a case for the reference case?

The impression of the above review of economic evaluations within the field of prevention and treatment of coronary heart disease is a very heterogeneous approach to perspective, time frame and use of data sources. Most studies applied the health care sector perspective, or similar, perhaps to some extent based on feasibility considerations. The heterogeneity in approach is not limited to the field of CHD, a similar image appears from other fields of health care research, e.g. in the field of aortic aneurysms, where cost-effectiveness analyses display different time frames and use of data sources\textsuperscript{157}.

The recommended reference case of the US Panel (described in Chapter II) differed from most of the reviewed studies\textsuperscript{56}, at least on their suggested perspective. The US Panel suggested application of the societal perspective, which, in their view, included only patient time costs outside the health care sector. The societal perspective was taken in seven of the reviewed studies. Amongst these, the definition of the societal perspective seemed to vary somewhat. One study included time costs in addition to health costs\textsuperscript{98}, as suggested by the US Panel, while three studies\textsuperscript{101;146;153} adopted the societal perspective which is
recommended by the Danish and Swedish health technology assessment guidelines\textsuperscript{64,65}. Three studies\textsuperscript{103,109,147} only included health care costs in their societal perspective.

The US Panel also suggested analysis over a sufficient time horizon in order to capture relevant costs and effects. A sufficient time horizon could be patient lifetime, which may only be feasible when a decision model is applied on the collected data. Indeed, most of the decision models reviewed took the lifetime perspective, while most studies without modelling applied a shorter time frame. Almost a quarter of the reviewed studies applied a time frame of five years or more, which may be sufficient. With regard to its recommended time frame, the reference case is adhered to much more extensively than was the case for the recommended societal perspective.

For data sources, the US Panel was more ambiguous in their recommendations, indeed they recommended that evidence for effectiveness may be obtained not only from RCTs and register data but also from uncontrolled experiments and expert opinions. In addition, modelling and meta-analysis can be applied when data or duration of data is insufficient\textsuperscript{41}. The Panel however retained good quality RCTs as their first choice for data for cost-effectiveness studies in health care.

While there may still be a rationale for a reference case for economic evaluations of health care interventions, the one suggested by the US Panel has not gained sufficient use to be a candidate. An international reference case is perhaps not very relevant, as decisions on health care interventions are nationally based and comparability of economic evaluations at the national level therefore should be prioritised. On the other hand, comparability of results with existing literature is an integral part of most evaluations and therefore some homogeneity is desirable. On the national level, recommendations exist for economic evaluations for health technology assessment in some countries. In the UK, NICE has issued a set of guidelines that are generally accepted for use in UK cost-effectiveness analyses\textsuperscript{63}. NICE recommends use of the NHS perspective for cost assessments, a clear deviation from the US Panel, and also from the rationale of the CEA that suggests a societal perspective, cf. chapter II. In Sweden, the Pharmaceutical Benefit Board also issued a set of guidelines differing from the US Panel in the opposite direction. Thus, the Swedish and Danish guidelines argue in favour of including also ‘indirect costs’ related to the intervention, productivity costs and gains following from the impact on life expectancy\textsuperscript{64,65}.

A modified reference case for economic evaluations of health care interventions could include: a sufficient time frame, a societal perspective, and data from good comprehensive data sources. This case has been
argued above, and is summarised as follows: the time frame should allow for all relevant costs and effects to be taken into account, in particular but not only for prevention interventions. The perspective should be societal in order to result in efficient resource allocations and include survivor costs in the acknowledgment that increased life expectancy incurs opportunity costs on others. Finally, in the words of Drummond et al (1997), the economic evaluation should be based on the best available data, and not necessarily the data originating from the top of the hierarchy. In fact, as it was argued in chapter III, for cost assessments, register-based data may be superior to RCTs, while the choice of data for effect measurement should be based on the efficacy-applicability trade-off.

The next chapter carries these points forward to a brief overview of the methods and data sources applied in this PhD.
In chapters II and IV, existing recommendations for economic evaluations were introduced and in particular the US Panel reference case was described and discussed. The Panel issued several recommendations, and a few of these with specific relevance for this PhD are further discussed below. According to the US Panel, adherence to the reference case suggests that an economic evaluation:

- Applies a time frame sufficient to capture all relevant costs and effects
- Analyse cost-effectiveness from a societal perspective albeit excluding productivity costs
- Use available data sources with good quality with RCTs as the first choice

While only one of the four papers that make up this PhD is an actual economic evaluation, all four papers are associated with economic evaluation in one way or another. The four papers are related to the above three elements of the US Panel reference case below.

**Time frame**

Coronary heart disease is a chronic, serious disease with a variety of long-term consequences. Therefore, assessment of costs and consequences should take the longer term into account. The recommendation by the US Panel, that the time frame should be sufficient to capture all relevant costs and effects is very important.

Paper 1 focuses on the lifetime health care costs of a new event of CHD and the additional costs of an unhealthy lifestyle. We only analysed costs however with the explicit aim of providing cost data for economic evaluation of preventive measures.

In paper 2, we analysed long-term labour market consequences of CHD. The register-based duration analysis allowed for assessment of consequences in up to 23 years after the index event. For some individuals the time frame was somewhat shorter, however the analysed time span was sufficient in order to draw conclusions on long-term consequences of CHD.

The economic evaluation in paper 3 concerned drug-eluting stents in coronary angioplasty. The study applied a time frame longer than most studies of the same topic. We had access to register-based data for
five years, and thus used a time frame fivefold that of the bulk of studies based on RCTs in the same field. The long time frame added important information to the study, as both costs and effects for the two compared treatments developed differently over time.

Paper 4 does not relate to coronary heart disease per se but does provide figures for future costs in an analysis with lifetime perspective. The analysis in paper 4 is based on the acknowledgment that future costs or survivor costs do play a role in cost-effectiveness measurement. The issue of survivor costs is examined in chapter II.

**Perspective**

Papers 1 and 3 apply the health care sector perspective, like most economic evaluations in the field. However, costs of heart disease and risk behaviour do occur outside the health care sector. Notably, paper 2 demonstrated that an event of coronary heart disease has important implications in the labour market.

It seems that there are two reasons why most economic evaluations choose to differ from the recommended societal perspective, one reason being that costs outside the health care sector are difficult to assess because there are measurement and valuation problems associated with these costs.

Another reason relates to costs from the societal perspective being difficult to define. In the view of the US Panel, societal costs include time costs of patients, and maybe future health and non-health consumption but not productivity changes. This distinction has been contested by a number of authors^{51,53,158}, as described earlier; also the Danish and Swedish recommendations for cost-effectiveness analysis deviate from the US Panel recommendations on this issue^{64,65}. In addition, the review in chapter IV demonstrated that the societal perspective was interpreted rather differently in the few studies that actually applied such a perspective. Paper 4 focuses on the implications of including all future costs in the cost-effectiveness analysis; that is, applying a societal perspective including productivity and consumption changes in the future.

**Data sources**

Above, it was described how economic evaluations can be based on RCT-data, register-based data, or extrapolated data from RCTs and registers. It has been argued that the choice of data should be based on considerations on efficacy versus applicability and not only adherence to a hierarchy. Paper 3 provides an
example of a register based economic evaluation while the other three papers are not economic evaluations *per se*. The analyses in all four papers are register-based.

The data source used in papers 1 and 2 is a cohort consisting of health interview survey data merged with register data\(^8\). The first survey was carried out in 1987 and the latest in 2005. For all respondents, a vast amount of register data on use of health care services, labour market behaviour, income, socio-economic and demographic parameters has been retrieved. In addition, the surveys include nationally representative information on HRQoL, lifestyle, self-reported health and use of health services etc. The cohort, consisting of these two data sources and covering a long period of time, thus provides a powerful source of data for use in economic evaluation.

As such a cohort enables for adjustment for a variety of covariates and includes a total of more than 30,000 individuals, it should not be considered inferior to RCTs as a tool for economic evaluation. Paper 1 used regression models with adjustment for a number of covariates to isolate the health care cost of heart disease and risk behaviour. Paper 2 used individual matching, where CHD-patients were matched with up to five individuals without CHD by means of various socio-economic and demographic characteristics. Using available covariates for confounder control does not prevent other factors from confounding results because the possibility of a confounder not taken into account will always exist, at least in theory. However all covariates that realistically could impact on results have been taken into account in the studies based on the DANCOS cohort\(^{13,16}\).

Paper 3 was based on a clinical database, thus it was also a register based analysis. Here as well, a number of covariates, clinical as well as demographic have been adjusted for. The economic evaluation in paper 3 is aimed at being applicable in the real world, as the data derived from everyday clinical practice. The study covered a field of vast RCT evidence, however there is no convincing evidence to support the use of drug-eluting stents in the literature\(^{159}\). The use of real life data in combination with the longer time frame in paper 3 provided a different perspective on the cost-effectiveness of drug-eluting stents.

Paper 4 used register information for the entire Danish population on income, production, health care, etc. It was not an economic evaluation but intended to provide data for use in economic evaluations. The analysis focused on 2005 data and thus provided a cross-sectional picture of production and consumption in the Danish population.
In the following chapters, the findings and key issues of the four papers are briefly introduced, before concluding on the main themes of this thesis.
VI. Costs of heart disease and risk behaviour (paper 1)

In this study, the attributable health care costs of heart disease were established. Furthermore, we analysed the additional health care costs for heart patients with risk behaviour before their first heart disease-related hospital admission.

The study was based on the notion that cost-of-illness estimates per se provide little guidance for decision making when applied outside the context of economic evaluations. However, economic evaluation of prevention programmes specifically targeted towards patients with heart disease may need cost figures of health care costs for patients with and without a history of heart disease. This study aimed therefore to inform decision-making about the cost consequences of risk behaviour amongst future heart patients.

The data for the study was derived from a cohort consisting of participants in a national representative health interview survey combined with comprehensive register based information. The register-based information about hospital diagnosis was used to identify patients with heart disease. We compared health care consumption amongst individuals who developed heart disease during 2002-2005 with health care consumption for individuals free of heart disease. We established the overall health care costs attributable to heart disease by use of linear regression with adjustment for confounding factors.

In addition, we estimated the attributable costs of excess drinking, physical inactivity and smoking amongst individuals that would become heart patients. Again, we adjusted for confounding factors and estimated attributable costs in a linear regression.

In the overall assessment of attributable costs, we found that individuals with heart disease on average cost the health care system €3,195 per person-year more than individuals without heart disease. This figure was statistically significant and presents a rationale for prevention of heart disease. Further, it reflects that heart disease is rather costly to the health care sector but also that other diseases related to the heart disease incur additional costs.
Amongst heart patients, individuals with a history of an unhealthy lifestyle incur higher health care costs than heart patients without a history of risk behaviour. The attributable cost of unhealthy lifestyle factors amongst individuals at risk of heart disease was 11-16 percent of the attributable cost of heart disease.

Heart patients with a history of excess drinking had health care costs of €503 more per person-year than heart patients without such history. For heart patients who previously smoked, the health care costs were €474 more per person-year than for never-smokers amongst heart patients. Physical inactivity in the past rendered a difference of €362 in health care costs per person-year. All figures were statistically significant.

The study provides a strong rationale for prevention of heart disease as well as risk behaviour, as it shows that heart disease incurs statistically significant additional costs to the health care sector, and more so if heart patients have a history of unhealthy lifestyle. Consequently, strategies to prevent or cease unhealthy lifestyle may not only result in cost savings due to avoided heart disease. Additional cost savings may be obtained because heart patients who prior to the disease led a more healthy life consume fewer health care resources.
VII. Short and long-term labour market consequences of coronary heart disease (paper 2)

This study focused on the labour market behaviour of individuals that have experienced CHD. Amongst survivors of CHD, some choose to leave the labour market as an immediate result of their disease. Most studies of labour market withdrawal however fail to take into account that CHD often occurs at an age where most individuals consider retirement anyway\textsuperscript{5-8;160-162}. It is therefore necessary to compare the labour market behaviour of CHD patients with a comparable reference group.

Also, the time frame of the analysis of labour market behaviour is often a year or less, however this does not take into account that some heart patients may return to work following their admission and subsequently retire earlier than they would have done had they not been ill.

This study, therefore, analysed to what extent individuals with coronary heart disease leave the labour market earlier than individuals without coronary heart disease in the short-term as well as in the long-term, and discussed the implications for rehabilitation.

We identified heart patients from the merger of health interview survey data and register data in the Danish National Cohort study\textsuperscript{89} and followed them from the year of their first hospital admission for coronary heart disease and onwards for up to 23 years. Individuals with coronary heart disease were individually matched with individuals without coronary heart disease. We analysed their short-term labour market participation and compared the long-term risk of labour market withdrawal for the two groups by means of Cox regression.

In the short-term, that is, the first year after the first coronary heart disease-related admission, 79 percent of heart patients maintained their labour market participation compared with 93 percent of individuals without coronary heart disease. In the long-term, heart patients had a hazard ratio of 1.32 for withdrawal compared with their matched counterparts, which was statistically significant. This means that heart patients were on the labour market, on average, for 0.8 years less than the individuals without coronary heart disease. Stratified analyses showed that, in particular, heart patients aged less than 60 years and
individuals employed as manual labour may benefit from cardiac rehabilitation, as rehabilitation aims to maintain and extend labour market participation\textsuperscript{10}.

The study showed that there remains a potential for cardiac rehabilitation to return heart patients to work and to maintain their employment status until they would otherwise have retired. In addition, greater focus in cardiac rehabilitation on returning individuals aged less than 60 in particular, and manual workers to the labour market might be worthwhile.
VIII. Painting the full picture: the case of long-term cost-effectiveness of drug-eluting stents (paper 3)

This study provides a case for the use of register-based data in economic evaluation and for taking into account the long-term costs and effects of a health care intervention. The topic of drug eluting stents has been thoroughly assessed in a variety of randomised controlled trials and thus studies with a high degree of internal validity. The longer term perspective has not been fully assessed yet despite the product being on the market for about 6 years.

Coronary angioplasty is a treatment of CHD in which a catheter widens a coronary artery which is blocked, by means of a balloon and leaves a stent in the artery in order to prevent it from blocking again. Paper 3 focuses on drug-eluting stents in coronary angioplasty. Drug-eluting stents were introduced about 2003 as an alternative to bare metal stents.

The bulk of literature in this field focus on short-term effects while the cost-effectiveness on the longer term seems to be rather unexplored. However, as the longer term costs and effects are highly relevant, for clinical practice as well as for decision making, we analysed the cost-effectiveness of drug-eluting stents in coronary angioplasty compared to bare metal stents over a five year period.

For this study, we obtained cost and effect measures from a database with observational data on patients receiving non-acute bare metal stents or drug-eluting stents. The data was joined with information from a patient survey on health related quality of life, and administrative data from the hospital. Taking into consideration that patient groups in an observational study may be less comparable than in a RCT, we adjusted for possible confounders in the analysis.

We identified differences in the outcomes of interest: repeat revascularisations and mortality by means of duration analysis. As the assumption of proportional hazards was violated, thus rendering Cox regression inappropriate, we used a Weibull accelerated failure time regression model for this analysis.
While QALYs were used as the effect measure in the CEA, the development of repeat revascularisations impacted on costs, and was analysed separately.

We used a Markov model to simulate the incremental cost-effectiveness using different time horizons. The incremental cost-effectiveness of drug-eluting stents over bare metal stents was €14,000 (CI –18,500 – 46,500) per QALY gained over five years. After one year, the time frame of many randomised studies, the incremental cost-effectiveness of drug-eluting stents, that is, the cost of achieving one additional QALY was prohibitively high.

In addition, the development in repeat revascularisations was different between the two types of stents over the five-year period, also pointing to the importance of a long analysis time frame.

Thus, the study provided an illustrative example of the profound impact of the analysis time frame. The two stent types displayed differing developments of effects over the five year period, adding to the argument of the sufficient time frame. Thus, while results after five years remained inconclusive on the recommended stent type, the expanded time horizon rendered important differences in the main finding.
IX. Future costs in cost-effectiveness analysis (Paper 4)

The topic of future costs in economic evaluations of health care interventions has been debated for almost two decades. Amongst the topics that have been discussed are application and definition of the societal perspective, notably the human capital approach versus the friction cost approach; whether productivity changes are captured by the QALY, and therefore should be excluded; and whether future unrelated health care costs should be included or not. Most recently, the debate has focused on changes in future consumption, and to a lesser degree production, following an increase in life expectancy.

Costs in cost-effectiveness analysis always include the so-called direct costs, costs directly related to the intervention; as well as downstream health care costs, at least within the study period. Most studies also include unrelated health care costs within the study period. The controversy pertains to the income effects of the increased life expectancy following from the intervention, consumption and production changes.

This study concentrated on the three components of future costs, or survivor costs: changes in health care consumption, changes in non-health care consumption, and changes in productivity following a health care intervention that increases the length of life of its participants. We introduced the term ‘net incremental consumption’ relating to changes in consumption (health care and non-health care) minus changes in productivity.

The aim of this study was to assess the magnitude of net incremental consumption in the Danish population using register-based data for one-year age groups; and to analyse the impact on the cost-effectiveness ratio of including net incremental consumption in the computation.

We used register-based data for the entire Danish population aged 16 and above in 2005. We defined production as gross earnings and subtracted any income from social security. Consumption was divided into health care consumption and non-health care consumption. We defined health care consumption as the share of health care paid for by the public authorities, including hospital treatment, treatment by general practitioners and practicing specialists, and the share of prescribed pharmaceuticals paid for by the authorities.
To assess the magnitude of non-health care consumption, it was necessary to make a number of assumptions, as individual consumption cannot be retrieved from registers. We assumed savings to be constant during productive ages, and consumption of public services other than health care to equal tariffs. Further, we assumed that individual consumption was evenly distributed within households. Consumption was then equal to disposable income, minus savings (during productive ages), plus an age-specific assumed consumption of public goods. This figure was summed for each household and divided by number of members in the household to obtain a measure of children’s consumption.

We calculated lifetime figures per age group, adjusted these for survival and discounted using a discount rate of 3 percent p.a., to obtain the net present value of net consumption in each age group. In addition, we computed costs per life year for application in a cost-effectiveness analysis.

The analysis showed that net consumption is positive (that is, consumption exceeds production) before age 20 and after age 65. Between age 20 and 65, production exceeds consumption and individuals in these age groups can be considered net contributors. The expected net consumption per added life year in a 30 year old person is more than €9,000, while the same figure in a 70-year old is €10,300 per added life year, equal to a difference of about €19,500 when these figures are included in the cost-effectiveness measurement.

As an example of the impact of including these figures in the cost-effectiveness analysis, consider the example of a bypass surgery in a 65 year old person. The surgery has a (hypothetical) incremental cost-effectiveness ratio of €15,000 per life year gained, compared to medical management. Inclusion of net incremental consumption would produce an ICER of €23,700 per life year gained, whereas the same intervention in a 40 year old has an ICER of €9,500, when net incremental consumption is included.

The results of the analysis point to the vast significance of age. The aim of economic evaluation of health care interventions is to aid decision makers in their prioritisation of interventions. Interventions aimed at younger patients will appear more cost-effective relative to interventions aimed at older patients, when future costs are included in the computation.
X. Conclusion

The high prevalence and important impact of CHD, as well as the presence of a wide range of interventions aiming to treat or prevent CHD make the rationale for analysing short as well as long-term resource consequences of the condition quite obvious.

This thesis has assessed and discussed the time frame, data sources and perspectives for analysing long-term costs and effects of interventions in the field of preventing and treating coronary heart disease. In the four papers, important resource consequences have been identified.

The rationale
The costs and consequences of CHD occur at multiple levels and at different points in time. I have argued that a comprehensive assessment of costs and other consequences of CHD should include the long term, which impacts other sectors than the health care sector. I have argued in favour of using the best available data for economic evaluations, and these may not be trial-based. Instead, use of register-based data is a feasible choice for economic evaluation and assessment of consequences of disease, because they provide a longer time frame than trials and their information on costs and effects resemble a real-world situation more closely. In addition, large registers and cohorts supply a larger data base than most trials, as well as information on a wide range of parameters so that results can be adjusted for possible confounders.

Findings
I have identified a number of advantages of using register-based data in economic evaluation. Compared to RCTs, the external validity, i.e. the applicability in clinical settings, is better in register-data. In addition, there are good opportunities for retrospective analyses of costs and effects over long time periods in register data.

In areas where RCTs appear difficult to conduct, there is a specific rationale for register-based analysis. Prevention of heart disease – or other diseases – is one such area. Generally, registers are as applicable for use in economic evaluations as RCTs, regardless of whether these registers are used alone or in combination with survey data. It should not be the conduction of the data collection that determines whether a data source should be used in favour of another; rather, the data source ought to be selected on
the basis of considerations regarding the number of individuals, the applicability for clinical practice and perhaps most importantly, the time frame of data.

In paper 1, we found that the health care costs attributable to CHD were significant and increased when individuals with heart disease had a history of an unhealthy lifestyle.

Paper 3 provided incremental cost-effectiveness ratios for a very widespread treatment strategy (drug-eluting stents), and demonstrated that an extended analysis time frame altered results significantly.

In paper 2, we found that CHD patients leave the labour market earlier than a comparable reference group, taking into account that CHD occurs at an age where many individuals consider withdrawing from the labour market anyway. The earlier labour market withdrawal points to the importance of the societal impact of CHD.

Figures for the societal impact of disease are often not readily available. In Sweden, average age group specific figures for survivor costs have been estimated with a view to application in economic evaluations\textsuperscript{166}. In paper 4, similar figures have been computed for Denmark, based on information at individual level on consumption and production in one-year age groups.

The analyses

I have demonstrated the feasibility of register-based data as well as the importance of a long time frame by using register-based data for assessing the short and long-term consequences of CHD through the four papers in this PhD. Papers 1 and 2 are based on a cohort comprised of respondents to the NHIS, which comprises survey information as well as comprehensive register information over a long time period. Papers 3 and 4 are register-based as well.

Paper 1 demonstrated that using incidence-based figures and the attributable cost approach provides an identification of health care costs that could have been avoided if CHD was prevented, or if individuals at risk of CHD had adopted a healthier life style.
In paper 2, adoption of a long time frame showed that there are long-term labour market consequences of CHD in addition to the short-term effect. Also, the register-based analysis provided the option of isolating the effect of CHD in labour market withdrawal, thus excluding the impact of age.

Paper 3 provides an example of an economic evaluation with a longer time frame than most studies in the field. Indeed, the findings changed markedly during the study period, thus making a case for the longer time horizon.

The results generated in paper 4 could not have been calculated by other feasible means than a register-based analysis. While adopting a cross-sectional view, the results of the analysis are presented with a view to application in evaluations with a long time horizon.

Challenges
Clearly, use of register-based data entails a number of challenges. Firstly, internal validity problems and possible confounders should be accounted for. Secondly, administrative registers do not include information on self-assessed health, lifestyle, or other self-reported parameters. Cohorts normally include these data; however as some cohort participants may not respond, the analysis could suffer from selection bias, as is the case for trial-based analyses as well. Therefore, whenever the analysis involves response or consent from participants, selection bias should be accounted for.

In Denmark, administrative registers have been widely used for several years. The data are used by researchers as well, in particular for health services research. Most registers are comprehensive as they cover the entire population, and of good quality since they have been validated and developed for several years. Thus, the health care registers include several variables over long periods of time, enabling researchers to use them for cross-sectional as well as time series analyses.

Administrative registers were not designed for research purposes per se. The main implication of this is that the quality of data may be too poor to base research conclusions on. The Danish health care registers have for several years not only been used for administrative purposes but also for remuneration of health care professionals. Therefore there has been a motivation for the professionals to enter correct and timely data into the registers. However, the limitations of the administrative data are important and should be taken into account.
Perspectives

It is important to apply a long time frame in future analyses of health care or health promotion interventions. This argument has been made with specific reference to CHD, although it applies to other diseases as well, in particular chronic conditions and lifestyle-related diseases. In addition, the societal perspective should be applied, if possible, as variations in life expectancy and HRQoL following a health care or health promotion intervention impact on future consumption and production which in turn has a societal effect beyond the individual concerned.

Therefore, the potential of using register-based data in economic evaluations, taking into account the caveats of such data, can still be expanded.
References


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Appendices

Paper 1: Costs of heart disease and risk behaviour

Paper 2: Short and long-term labour market consequences of coronary heart disease


Paper 4: Future costs in cost-effectiveness analysis