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How to include relatives and productivity loss in a cost-effectiveness analysis

- theoretical and empirical studies

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To Lee Ti

To include, or not to include:
that is the question

Travesty on the lines in Hamlet,
Shakespeare (1564-1616)

Contents

ABSTRACT

Health economic evaluations are today commonly used in the decision-making process in health care. Within the field of cost-effectiveness analysis (CEA), there are several methodological and empirical issues that cause debate about what is included in the analysis. This thesis covers two such issues; costs and effects for relatives, and the valuation of individuals' productivity loss due to morbidity. The objective of the thesis is to provide further knowledge about what should be included in CEAs which take a societal approach. The papers that the thesis is based on, four in total, examine the theoretical aspects of the studied issues and test these aspects empirically. Three different data materials were used. The CEA and the estimation of costs and effects are central in all the papers. The outcome measure used is quality-adjusted life years (QALYs).

The relatives of an individual with a disease or disability often provide informal care, and there may also be concomitant effect on their own well-being. Nevertheless, the costs and effects for the relatives are generally excluded from CEAs, and there are few guidelines for how to include relatives' effects. This thesis suggests the use of a new measure, R-QALYs, which can be used both to visualise relatives' effects and to include them in the analysis. We found that while the EQ-5D instrument can be used to capture some of the relatives' effects, it most likely misses a number of important attributes, for example altruistic preferences. Methods of eliciting R-QALY weights include direct valuation methods and indirect methods, using existing relative-related instruments. However, none of these methods are without difficulties, and there is a need for more studies on estimating valid relatives' effects. Another possible approach with high potential is to use monetary measurements for both the costs and effects relevant to relatives.

The results also show that income affects the QALY weights if the individuals include the utility generated by consumption within their QALY weights. The empirical tests showed that a majority of individuals do not consider their own income when they value health states. An explicit instruction to take income into account seemed to affect the valuation of those health states that were assumed to have consequences on the ability to perform daily activities.

These findings give support for including the productivity costs caused by morbidity in the analysis; as these costs are not, or are only to a minor extent, implicitly incorporated in individuals' QALY weights. The loss of leisure time, however, is captured in the QALY weight, and care must be taken to avoid double counting this loss in the analysis.

The results of CEAs will only be partial if relatives' costs and effects and the costs of individuals' productivity loss are excluded for health interventions where they are assumed to be of significant importance.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Davidson T, Levin L-Å
Is the societal approach wide enough to include relatives?
- Incorporating relatives' costs and effects in a cost-effectiveness analysis.
Submitted

II. Davidson T, Krevers B, Levin L-Å
In pursuit of QALY weights for relatives
- Empirical estimates in relatives caring for older people
European Journal of Health Economics, (2008) 9:285-292

III. Davidson T, Lyth J, Janzon M, Levin L-Å
Direct valuation of health state among patients with chest pain
- Does income level matter?
*S*ubmitted

IV. Davidson T, Levin L-Å
Do individuals consider expected income when valuing health states?
International Journal of Technology Assessment in Health Care, (2008) 24(4):488-494

ABBREVIATIONS

CA	Conjoint analysis method
CAL	Costs of added life years
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CV	Contingent valuation method
EQ-5D	EuroQol-5 dimensions
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
NICE	National institute for health and clinical excellence
QALY	Quality-adjusted life year
QoL	Quality of life
R-QALY	Relatives' quality-adjusted life year
RS	Rating scale
SEK	Swedish kronor (currency in Sweden)
TLV	The Swedish dental and pharmaceutical benefits agency
TTO	Time trade-off
VAS	Visual analogue scale
WTP	Willingness to pay

BACKGROUND

Introduction

Resources in the society are scarce. This is also true for the health care sector, and there are reasons to believe that the gap between demand and supply within health care will increase. There are three main reasons for this. Firstly, new health care technologies are constantly being invented, implying that more diseases or disabilities can be treated. Secondly, there is an ongoing demographic transition in most western economies leading to an increasing proportion of elderly people within the population. Finally, the emergence of more accessible information creates higher public expectations. [1-4] As it is often the case in western economies that the major part of health care costs is paid by society, there is a need for societal priority setting. The resources available are not sufficient to cover all possible treatments, and so it is necessary to direct these resources towards the most effective treatments. Health economic evaluations are a useful tool in making these prioritisations, as they provide information about the costs and health consequences generated by medical technologies.

Health economic evaluations are commonly used in the decision-making process today. For medical drugs to receive reimbursement by government, they must often be proven to be cost-effective [5-7]. Health economic evaluations can also be used to compare the cost-effectiveness of different treatments for different medical areas. This can help decision makers gain knowledge about which areas and methods should be prioritised higher than others.

Health economic evaluations should include all costs and effects stemming from the medical technology being assessed within the chosen perspective. However, in practice this is not an easy task. The main reason is that imperfect methods for estimating costs and effects cause debate regarding which aspects are actually included in the evaluation. Another reason is that external effects may occur due to a medical treatment, which could lead to unobservable costs and effects.

Health economic evaluations have only been in common use for a few decades, and there are reasons to believe that they will continue to be altered and improved in order to better guide the decision makers. The most commonly used type of evaluation is the cost-effectiveness analysis (CEA), and this analysis is therefore the focus of this thesis. There are several methodological and empirical issues within the CEA that cause debate about what is included in the analysis, and are in need of more research. Two of these issues are covered in this thesis:

(a) How costs and effects for the relatives of an individual with a disease or disability should be considered in the analysis

(b) How individuals' productivity loss generated by morbidity should be considered in the analysis

Both issues depend to a large extent on what individuals include in their valuations of health states, and they furthermore comprise important methodological issues in the CEA. These areas are therefore linked to each other.

Costs and effects for relatives

An individual's disease or disability often also affects his or her relatives; these effects can be referred to as external effects. The relatives may provide informal care, and there may also be effects on their own well-being [8]. Hence, medical treatments also affect the relatives, and so an analysis of a medical intervention must also include the costs and effects incurred by the relatives. It has already been shown that if a sick or disabled individual's quality of life (QoL) is improved, the relatives who provide informal care to that individual can often reduce their caregiving time and also improve their own QoL [9]. It has furthermore been argued that there are spill-over effects within a family, indicating that each family member's QoL is affected by that of the others, and hence that health economic analyses should consider these effects when a medical technology is evaluated [10]. The estimation of relatives' costs and effects will be thoroughly explained further on in this thesis.

There are several studies showing that relatives who provide informal care are often affected in a number of ways by the cared-for individual's disease or disability [11-21]. In general, these studies define these effects in terms of QoL or burden of care. Effects on relatives' QoL have been shown to depend on characteristics of both the relative and the cared-for individual, such as age, gender, and severity of diseases, and also on factors such as the caregiving situation and the surrounding environment [21, 22]. The effects on relatives' QoL may be positive [23-25], even though the negative aspects often dominate [21]. The negative aspects may include feelings of being overwhelmed, trapped, angry, anxious, and torn between caregiving and other responsibilities [21]. Providing informal care has even been shown to increase mortality for the caregivers in some cases [26, 27]. The positive aspects of providing informal care include for example the feeling of being appreciated by the cared-for individual, spending time together, and so on [23, 24]. Nolan et al. [25] argue that the key concepts in the satisfaction of caring are reciprocity, relationships and meanings. Brouwer et al. [24] have described the positive aspects from providing care as process utility, and stated that this utility is often high when the care is provided on a voluntary basis. Jacobson et al. [28] found that both positive and negative aspects of providing informal care (which they refer to as caring externalities) are related to severity of the disease for the individual.

It is particularly important to consider relatives' costs and effects when the relatives are actively involved in the individual's health situation, or provide a great deal of informal care. In the case of stroke, schizophrenia, or Alzheimer's disease, for example, a large portion of the costs and effects of the disease are carried by the individual's relatives [17, 18, 21]. Relatives' costs and effects may also be of special importance in the context of children with serious diseases [20] and in caring for older people [29]. Informal care has been estimated to constitute for 9.3% of all costs associated with dementia care in Sweden [30]. It has earlier been assumed that about 10 to 20% of adults in Sweden give care or support to somebody [31], which illustrates the extent of informal caregiving. However, only a minority of all health economic analyses have considered the relatives [32]. It is therefore important to put more emphasis on relatives' costs and effects in health economic evaluations. There are, however, methodological challenges concerning how these external effects should be measured and included.

Productivity loss

Any health economic analysis taking a societal perspective should include the productivity loss caused by morbidity or mortality. However, in a study on the cost estimation of published CUAs, only 8% of the analyses included productivity costs [32]. One reason for this low number is that there are questions regarding how this cost should be included in the analysis [33, 34]. If an individual's productivity loss leads to income loss for the individual, and he or she takes this loss of income into account when valuing health states, this means that part of the productivity loss (the income loss) is already included in the analysis. In this case, separate inclusion of the cost of productivity loss would lead to double counting. Conversely, if individuals do not consider income in their valuation of health states, productivity loss should be included as a cost in the analysis.

The issue of whether individuals consider their income in their valuation of health states also has consequences regarding the inclusion of the costs of added life years (CAL). If a medical technology leads to increased life years, then there are generally costs associated with those years. These costs do not necessarily increase the total costs, as they are the net of future consumption and future production. For the elderly, however, CAL generally increases the total costs. There are a number of different opinions concerning the theoretical arguments for including CAL in the analysis [35-37]. Nyman [38] focuses on the internal consistency argument; that the benefits in an analysis must be consistent with the factors counted as costs in the same analysis. Following this argument, CAL should be included in the analysis if the utility of consumption is included in the valuation of health state. Nyman [38] writes that the most common methods for valuing health states do not capture consumption, and that CAL should therefore be excluded from the analysis. Conversely, others [39, 40] argue that the internal consistency argument leads to the inclusion of CAL in the analysis, as the health state valuation implicitly assumes normal consumption.

Different analyses often include various types of costs, which may bias the results and make comparisons between different studies difficult. It is therefore important to investigate what individuals actually consider in their valuations of health states, as this affects the costs that should be included in the analysis.

Cost-effectiveness analysis

The issues studied in this thesis share the same theoretical background concerning health economic analyses. There are four main types of health economic analyses; cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). CEA and CUA share the same structure, and can therefore be seen as the same type of analysis. The difference between the two is that a CEA can use any outcome measure, while a CUA uses quality-adjusted life years (QALYs). In the rest of this thesis, there will be no distinction made between these two, and the term "CEA" will be used exclusively. Furthermore, the work presented here is concerned with the CEA alone, and not the CMA or CBA, due to its dominance in the health care decision-making process.

In a CEA, the additional (incremental) costs generated by one medical treatment compared to another one are estimated and then put in relation to the additional (incremental) outcome. This generates a ratio between incremental costs and effects, known as the incremental cost-effectiveness ratio (ICER), (see Figure 1).

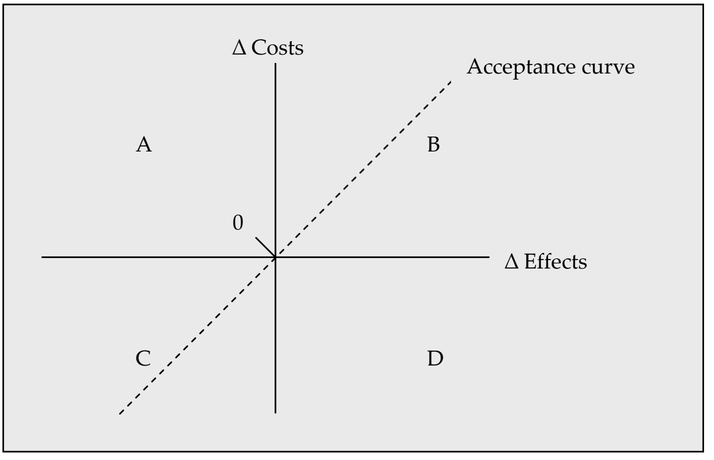
Figure 1. The incremental cost-effectiveness ratio (ICER)

$$\frac{\text{Costs}_A - \text{Costs}_B}{\text{Effects}_A - \text{Effects}_B} = \frac{\Delta\ \text{Costs}}{\Delta\ \text{Effects}} = \text{ICER}$$

The ICER includes costs in the numerator and effects in the denominator, and shows how much extra it would cost to receive one extra effect unit for one treatment compared to another. The costs are expressed in monetary values, and the effects can be estimated in any relevant outcome measure, such as complications, ability to move, objective or subjective measures of QoL or life years, and so on. Generic outcome measures such as life years are preferable, to allow for comparisons between other analyses of various medical technologies and to provide decision makers with useful information. However, if the intervention also affects morbidity, life years alone will not capture this; instead, QALYs are often used. QALY is a measure which combines the value of the health state with life years, and will be explained more fully later in this chapter. When both costs and effects are included in the analysis, there is a risk of double counting; that is, of the same aspect being included both among the costs and among the effects, and therefore counted twice.

The result of a CEA (the ICER) can be illustrated in a cost-effectiveness plane (see Figure 2). The horizontal axis represents the incremental effects between the assessed treatment and the comparator, while the vertical axis represents the corresponding incremental costs. If the ICER is located in the northwest quadrant (A), then the treatment is both less effective and more expensive compared to the alternative treatment, thus the assessed treatment is dominated by the comparator. If the ICER is located in the southeast quadrant (D), then the treatment is more effective and less costly than the alternative treatment, thus it dominates over the comparator. The ICERs of new treatments are commonly located in the northeast quadrant (B), which means that the assessed treatment generates higher costs but also gives better effects compared to the other treatment. To find out whether this treatment can be assumed to be cost-effective, it is necessary to add a line symbolising the threshold value for an increase in effects. If the ICER of a treatment is below this acceptance curve, it is accepted as a cost-effective treatment. If the ICER of a treatment is located in the southwest quadrant (C), then the assessed treatment is cheaper but less effective compared to the alternative treatment. The acceptance value for an effect should represent the societal willingness to pay (WTP) for the effect. The value can be set at different levels, and it can also move depending on the situation. There is no true societal value that can always be used, though threshold values may be decided by the decision makers to simplify the priority setting process.

Figure 2. The cost-effectiveness plane



Perspective and theory

It is often recommended that a CEA should use a societal perspective [34, 41], indicating that all costs and effects arising from an intervention should be considered, no matter where, when, or for whom they appear. The societal perspective is not, however, the only possible perspective. The goal may instead be to maximise the health outcome from a given budget, as this is the most typical situation for decision makers in health care, and in this case costs that do not affect the health care budget should not be included in the analysis. An example of such costs is the productivity loss caused by morbidity or mortality. There are also other possible perspectives, such as a hospital, patient, or a third-party payer's perspective. Only the societal perspective, however, will lead to optimal decisions for the society as a whole.

Health economic analyses are largely based on the theories of neoclassic economics (welfare economics) which generate arguments for using a societal perspective. Welfare economics assumes that the welfare (or utility) of the society is the sum of all the individuals' welfare (utilities). Furthermore, it is assumed that all individuals strive to maximise their utility, that every individual is assumed to know best how to maximise his or her own utility, and that the utility is expected to be a function of the commodities consumed by the individual. By aggregating all individuals' utilities, the total societal utility is reached.

In this thesis, a societal perspective based on the theories of welfare economics is chosen as the starting point. The methods discussed and used in this thesis are therefore mainly those supported by the theories of welfare economics. However, in practice, decision making in health care must accept some departures from welfare economics. For example, while welfare economics supports the use of a CBA, this is difficult to use in practice in the field of health care, and instead the CEA is preferable. Therefore, in this thesis, the CEA is accepted as the dominant method, and the research focuses on how the CEA can be more accurately based on welfare economics.

Cost estimates

There are three main phases in estimating the costs of a treatment; identifying, quantifying and valuing. In the first phase, all direct and indirect costs that are affected by a treatment should be identified. This includes the cost of the treatment itself, time used by doctors and nurses, and so on. It may also include the costs of adverse events, future costs, informal care, productivity loss, and other factors. In the second phase, suitable measures are selected and used to quantify all the identified costs, such as minutes of doctor's time, hours of informal care, hours of paid productivity loss, and so on. Finally, all costs need to be valued to be used in the CEA. All costs should be presented in monetary units, meaning that aspects such as the time used for treatment and the doses of drugs must be valued monetarily. The resources used should be valued at their opportunity costs, which is the value of their best alternative use. As market prices often do not exist within health care, it may be necessary to find the opportunity costs in other ways. If the costs occur in the future, they also need to be discounted to their present value. None of these steps in estimating the costs is without its difficulties, and there is much to say about each step; this thesis, though, only presents this briefly. Some types of costs are particularly relevant in this thesis, however, and so are further explained here; specifically, the costs due to informal care and to productivity loss, and the costs associated with added life years.

Cost of informal care

Informal care is care provided by an individual's relatives or friends who are not paid for the services. The cost of this care should be included in the analysis, and informal care therefore needs to be identified, quantified and valued. The two main methods used for quantifying the time used for informal caregiving are the diary method and the recall method. Comparative studies have shown that the recall method may give a higher estimate of informal care hours [42]. Both the diary and the recall method can be supplemented with questions about what kind of care is provided, in order to reduce the risk of joint production. Joint production occurs when the informal caregiver performs activities that benefit himself or herself while providing informal care, and this should be deducted from the cost of informal care.

The opportunity cost method calculates the costs of informal care as the value of the best alternative use of the time used for informal care. If the caregiving hours could be used for formal (paid) production, the value of informal care is equal to the value of this production. If the informal caregiver uses his or her leisure time, then the cost of informal care is equal to the value of this leisure time. Another method is the shadow price method or the proxy good method [43], which aims to find the price of a service that has no market price. In estimating the cost of informal care it has also been suggested that the informal caregivers' well-being should be measured [8, 44]. This could be done by measuring their burden of caregiving or their health-related QoL. In this thesis, the term "relatives' effects" is used for these effects on well-being; the term "relatives" is used rather than "informal caregivers", as people other than the informal caregivers may also be affected by the individual's disease or disability, and "effects" is used rather than "well-being" in order to be consistent with the terminology of the CEA.

The cost of informal care has been discussed in several articles (see for example [45-51]), but there is still a need for more research into the methods for measuring and valuing this. Furthermore, relatives' effects are only rarely studied and discussed in health economic research, and there is a large gap to fill if we are to be able to give clear guidance on how to consider this information in a CEA.

Most of the studies that have estimated the cost of informal care have included the loss of formal production. The value of lost leisure time is excluded, which means that most calculations of informal care underestimate the true societal cost. This may have consequences for the accuracy of the results, as it is likely that most caregivers begin by reducing their leisure time when they start providing care, and only reduce their paid productivity if the caregiving situation becomes time-intensive. During recent years, a number of other methods, some of which also capture lost leisure time, have been used to estimate the cost of informal care. There have been some attempts to estimate the costs of informal care using the contingent valuation (CV) method [50, 52, 53] and the conjoint analysis (CA) method [49, 51, 54, 55]. With the CV method, one tries to find the relatives' WTP for someone else to provide the informal care. In the CA method, the value of the informal care is derived from studies where the caregivers choose between caregiving situations with different attributes, such as type of informal care, number of caregiving hours, and monetary compensation. A newly developed well-being valuation method [56] has also been suggested. In this method, the value of an additional hour of informal care is found by estimating how much compensation the informal caregiver would need in order to maintain the same level of well-being [57].

Productivity loss

Productivity costs have been defined as costs associated with productivity loss and replacement due to illness, disability, and death of productive persons, both paid and unpaid [58]. Other definitions have also included the value of lost leisure time [34]. The value of the productivity loss is estimated by the opportunity cost method, generally with the human capital approach. This approach assumes that the value of one individual's production is equal to the cost of having the individual employed, which is the salary including social taxes and fees. The human capital approach is used as the employer in a market economy is assumed to employ additional people until the value of the last person's production is equal to the cost of having that person employed. It has, however, been argued that the human capital approach overestimates the true societal costs, as there are always unemployed workers who can replace the sick or disabled person. Therefore, another method, called the friction cost method, has been recommended [59]. The proponents of this method argue that productivity loss only occurs during a certain time (the friction time) before another (previously unemployed) person can achieve the same production.

The definition of productivity costs also includes the value of unpaid production. The productivity loss of lost unpaid production should be valued as the individuals' own valuation of this time [60]. Methods such as revealed preferences, the CV method, or the CA method could be used to find this value.

The productivity loss could either enter the CEA as a cost, placed in the numerator, or be included in the outcome measure, depending on what the outcome measure (QALY) actually captures. While some argue that QALYs are affected by individuals' income [34], other claim that the methods used for eliciting QALYs do not capture income effects [58, 61]. There is a link between income and health, in that both life-years and QALYs are positively correlated with income [62]. However, it is still unknown whether income affects the elicitation of QALY weights. Donaldson et al. [63] argue that income is an important determinant of non-monetary valuations such as QALYs, but they did not test the strength of this relationship. Lost leisure time caused by the same morbidity is, however, more easily captured in the QALY weight [64], which is the reason why the first definition of productivity cost excluded lost leisure time [58].

If the methods to elicit QALY weights are affected by income, this would support the inclusion of CAL in the analysis. The estimation of CAL should include both the cost of the consumption and the value of the production that is generated during the added life years.

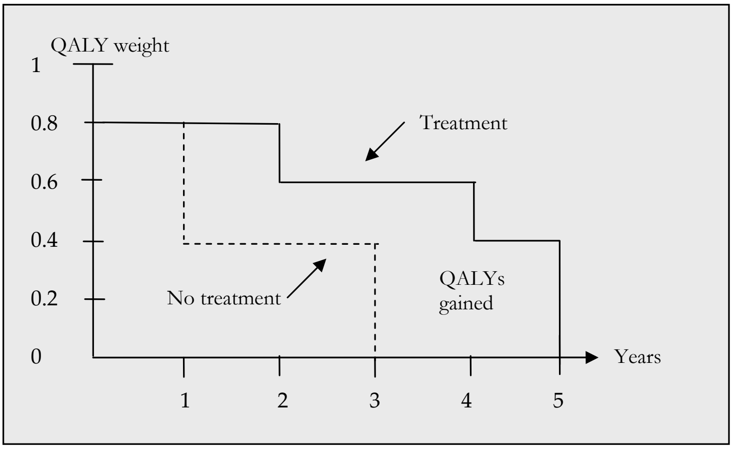
Valuation of health state

Both areas of focus within this thesis, costs and effects for relatives and valuation of productivity loss, are related to the methods of valuing a health state. On the basis of welfare economics, the preferable outcome measure should represent the individuals' preferences for health. The theoretically most accurate method of eliciting a value is to use individuals' WTP for the treatment. However, this is not applicable in a CEA. Individuals' preferences for health states are instead estimated by trying to measure their utility generated by the treatments. As medical treatments generally try to improve the individuals' well-being or QoL, this is assumed to be of importance for the individual's utility, and so the patients' QoL must be measured. Both health and QoL consist of several characteristics, and so it is necessary to define those characteristics that are relevant to the decision problem being studied. Health-related QoL is often used in order to capture only those QoL-characteristics that are directly derived from health [65].

Quality-adjusted life years (QALYs)

The most commonly used outcome measure for health is the QALY, which combines life years with the value of the health states during these life years. One QALY reflects living one year in full health. The QALY weight represents the value of the health state, with 0 and 1 describing death and full health respectively. To calculate QALYs, one multiplies the QALY weight by the number of years spent in that health state. For example, if a treatment means that a patient will survive another 10 years with a QALY weight of 0.6, this generates 6 QALYs. Another example is illustrated in Figure 3. In this case, a patient who undergoes a treatment is expected to live 5 years, while an untreated patient is expected to live 3 years. Furthermore, the treatment increases the patient's health-related QoL (the QALY weight), as illustrated by the thick line. The alternative treatment is illustrated by the dotted line. The number of QALYs gained is the area between the two lines, and it can be calculated as $(2 \times 0.8 + 2 \times 0.6 + 1 \times 0.4) - (1 \times 0{,}8 + 2 \times 0.4) = 1.6$ QALYs undiscounted. If a 3% discount rate is used for the future years, the QALY gained is 1.48.

Figure 3. Illustration of quality-adjusted life years (QALYs)



The use of QALY as outcome measure is based in welfare economics under certain conditions, based on the theory of expected utility. In the 1940s, von Neumann & Morgenstern [66] extended the theory of how individuals strive to maximise their utility to also include uncertainty. They took a normative approach and prescribed how rational individuals ought to behave in situations with uncertainty (which may be different from how they actually behave). They put up six fundamental and necessary axioms that must be fulfilled for the theory to be valid. Based on these assumptions, Pliskin et al. [67] developed a theoretical framework for QALY. They stated three assumptions that must be fulfilled for a QALY to be a valid cardinal utility function, which means that QALYs can be estimated and aggregated over all relevant individuals to find the total utility generated from a treatment. These assumptions are; mutual utility independence between life years and the QALY weight, constant proportional trade off property, and risk neutrality over life years. However, studies have shown that these assumptions do not hold in practice [68]. Cohen [69] argues that these assumptions are especially hard to satisfy for medical decisions, because they are one-time decisions which are not repeated.

Valuation methods

There are both direct and indirect methods of eliciting QALY weights. The main direct methods are standard gamble (SG) [66], time trade-off (TTO) [70], and rating scale (RS). SG is built on the theories of expected utility under uncertainty, and is the only valuation method that includes risk attitudes. When using SG, the respondents are asked to choose between living in their current health state, and living with full health but with a risk of immediate death. The risk is varied until the respondent is indifferent between the two alternatives. The QALY weight of the current health state is then equal to the chance of living in full health at the point where the respondent is indifferent between the two alternatives. With the TTO method, respondents are asked to choose between living a certain number of years in their own current health state and living a reduced number of years in full health. The trade-off is varied until the respondent is indifferent between the two alternatives. Unlike the SG, TTO will not capture individuals' risk attitudes but instead capture their time preferences. Both SG and TTO have a theoretical foundation for estimating the QALY weights [71, 72]. Both methods would furthermore theoretically generate the same result, which is valid for any number of life years as long as QALY is a valid cardinal utility function [41].

With the RS, respondents are asked to mark their valuations on a cardinal scale. A visual analogue scale (VAS) is often used for this purpose. A VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end. When a VAS is used to value health states, the endpoints could range from worst imaginable health to best imaginable health. The respondent is asked to mark on the line the point that they feel represents their perception of their current health state. RS is easy to use, but has some theoretical weaknesses, and is difficult to interpret satisfactorily for the creation of QALY [41] because the respondent does not have to make a choice that reveals their true preferences.

There are also indirect methods for eliciting QALY weights. With these, the respondent answers an instrument consisting of a battery of questions. A health profile (or index) is calculated from the answers, and then associated with a certain QALY weight which has been found earlier by means of SG, TTO or RS. Some commonly used indirect methods are the questionnaires EQ-5D [73], SF-6D [74], and health utilities index (HUI) [75]. Of these, EQ-5D is probably the most commonly used. EQ-5D is a generic health-related QoL-instrument which includes five questions representing five dimensions of health: *mobility*, *self-care*, *usual activities*, *pain/discomfort*, and *anxiety/depression*. In every dimension, the respondent can choose one of three levels: *no problems*, *moderate problems*, or *severe problems*. The answers are used to generate a health state index, representing the respondent's health-related QoL. A total of 243 health states are possible, and each health state is associated with a value found by direct methods (TTO and VAS) and representing preferences for the health states from a community perspective. Official values currently exist for 8 countries [76], and this number is likely to increase. The first established values (and still the most commonly used ones) represent a British community perspective [77]. The EQ-5D Instrument also includes a modified VAS (EQ-VAS).

The use of guidelines

As a consequence of the increased use of health economic analyses in the decision-making process, a number of guidelines for how to perform these analyses have appeared. These guidelines come from the academic field [41, 78] as well as from governmental organisations which need to make decisions in health care [5-7]. Due to the different backgrounds and purposes of these guidelines, they may differ in several aspects. However, as health economics research has developed, it has become increasingly possible to ground these guidelines in both theoretical and empirical findings, and so different guidelines have become standardised in many aspects. In some areas, however, they still differ. For example, several guidelines recommend the use of a societal approach for health economic analyses [34, 79, 80], while others recommend a health care perspective [5, 6]. One example of the latter is in the UK, where the National Institute of Health and Clinical Excellence (NICE) has recommended an approach that focuses on maximising the outcome from a health care perspective, as NICE cannot influence the size of the health care budget [6]. The guidelines also partly differ in the issues studied in the present thesis, mostly due to the lack of empirical findings.

Most guidelines comment on the need to include informal caregiving as a cost, but do not explicitly argue for including any effects incurred by the relatives. However, the cost of informal care is not relevant in a health care provider perspective. Some guidelines furthermore specifically mention the relatives' consequences caused by giving informal care [6, 7, 34]. The Swedish dental and pharmaceutical agency (TLV) [7] state in their guidelines that those costs and revenues that fall upon relatives should also be included in the CEA, as a consequence of the recommended societal approach. The Panel on cost-effectiveness in health and medicine in the USA [81] has also encouraged analysts to think broadly about the relatives, and to include where necessary the health-related QoL effects of significant others in sensitivity analyses. The NICE guidelines [6] state that the "perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers)".

Following the societal approach, most guidelines recommend the inclusion of productivity loss as a cost in the CEA [5, 78, 79]. However, the guidelines of the panel in the USA [82] argue that the value of these costs are captured in the estimation of QALYs, and hence that these costs should not be included in the numerator of the CEA as this would lead to double counting. Just as the productivity loss due to mortality is included in life years or QALYs gained, they argue that this is also the most appropriate method for productivity loss due to morbidity. They also state that if the methods that are used for eliciting QALY weights do not capture loss of income, including the productivity loss for relatives and friends, then these costs must be included in the numerator [83]. The Canadian guidelines for the economic evaluation of health technologies [5] state that in the valuation of health states, respondents should be told to assume that health care costs and income loss are fully reimbursed, in order to ensure that no income effects are captured among the effects.

There are also different recommendations concerning the existence of CAL in the analysis. TLV [7] in Sweden recommends that CAL should be included in the analysis whenever a treatment affects life expectancy. The panel in the US [82] recommend that CAL should be included in sensitivity analyses whenever they make a significant difference to the analysis. Finally, the WHO guide to CEA [84] recommends that these future costs should be excluded, as it is impossible to determine the relationship between the net changes in non-health consumption valued in money terms and the resulting changes in welfare.

AIMS OF THE THESIS

The objective of this thesis is to provide further knowledge about what should be included in cost-effectiveness analyses from a societal approach. It includes studies on costs and effects for relatives, and studies of the valuation of individuals' productivity loss generated by morbidity. It has four main aims:

- To examine and discuss how relatives' costs and effects could be measured, valued, and incorporated into a cost-effectiveness analysis. (Paper I)

- To illustrate and estimate relatives' QALY weights for relatives caring for an older person for at least four hours a week. (Paper II)

- To test whether individuals' incomes can explain their valuations of their own current health states generated by TTO and RS, by studying the theoretical aspects as well as via empirical testing. (Paper III)

- To examine whether individuals take their expected income into consideration when directly valuing hypothetical health states. (Paper IV)

MATERIAL AND METHODS

This thesis is based on four papers which examine the theoretical aspects of the studied issues and also test them empirically. Three different data materials were used. The CEA and the calculation of costs and effects are central in the papers, and a societal perspective was generally chosen. Papers I and II cover costs and effects for relatives, while papers III and IV cover individuals' valuation of productivity loss (Table 1).

Table 1. Overview of the papers in the thesis

	Costs and effects for relatives		Productivity loss	
	Paper I	**Paper II**	**Paper III**	**Paper IV**
Theoretical:	X	-	X	-
Empirical:	-	X	X	X
Data material:	Literature	EUROFAMCARE N=921 (Relatives)	FRISC-II N=156 (Patients)	Data collected from students N=200 (Students)
Main question of the paper:	How should relatives' costs and effects be included?	Can relatives' effects be found using the EQ-5D instrument?	What is the relationship between income and valuation of health state?	Do individuals consider their income in their valuations?
Overall focus:	What is included in QALY?			

Costs and effects for relatives

Two studies investigating the costs and effects of relatives are included in this thesis. The first addresses the question of how to value and include the costs and effects for relatives in the CEA. The second is an attempt to measure relatives' effects with the EQ-5D instrument.

Paper I

The intention of paper I was to discuss the role of including relatives' costs and effects in a health economic evaluation, and to examine how costs and effects for relatives can be measured and included in a CEA. Theories for the CEA were explored, along with choice of perspectives and measurement methods, and the question of whether the measures are capable of capturing relatives' costs and effects. As part of this, we conducted a search for a theoretically and methodologically acceptable approach to include all relatives' costs and effects, and introduced a new measure, the R-QALY weight, defined as the effect on a relative's QALY weight due to being a relative to a disabled or sick individual. This paper was based on a literature review and on further development of the health economic tools.

Paper II

Paper II was based on data from the Swedish arm of the EUROFAMCARE study [85, 86]. One aim of EUROFAMCARE was to explore the situation of family carers of older people in relation to the existence, familiarity, availability, use, and acceptability of supporting services in six European countries. EUROFAMCARE started in January 2003 and ended in December 2005. Relatives caring for or supporting an older person were interviewed in Germany, Greece, Italy, Poland, Sweden, and the United Kingdom. Almost 1 000 interviews with relatives caring for or supporting an older person were conducted in each country, either by telephone or by personal meeting. A common protocol with structured questions was used in all countries. The inclusion criterion was that the relative should be caring for or supporting an older person (over 65 years) for at least 4 hours a week.

A total of 921 interviews with relatives were conducted by telephone in Sweden. Out of these, 886 relatives (94%) consented to be contacted one year later, at which time they were asked to fill in a follow-up postal questionnaire; 575 (67%) of them responded to this questionnaire, 371 (64%) of whom still met the inclusion criterion of providing care for at least 4 hours a week. The Swedish part of the study was approved by the ethics committee at the Faculty of Health Sciences, Linköping University.

The characteristics of the sample are presented in Table 2; the interview study is named T1, while the follow-up study is named T2. The most frequent diseases or impairments found among the older people were general weakness due to old age, stroke, dementia, musculoskeletal diseases, and cardiovascular diseases. More than 50% of the older people had two or more diseases/impairments. More than 40% of the sample provided less than 10 hours of care or support per week, while 30% provided more than 40 hours of care or support per week, indicating a large variety in the caregiving situation of the studied sample, as had been intended when planning the study.

Table 2. Characteristics of the EUROFAMCARE sample

Sample:	**T1**	**T2**
Year:	2004	2005
N:	921	371
Sex:		
Men	28% (257)	29% (107)
Women	72% (661)	71% (262)
Age:		
Mean age:	65.4	66.5
Mean age: Men	68.3	70.1
Mean age: Women	64.3	65.1
Hours of care per week:		
4	17% (152)	12% (41)
5-9	25% (225)	27% (95)
10-19	16% (145)	18% (64)
20-39	12% (113)	15% (53)
>40	30% (279)	29% (103)
Relationship to the older person:		
Spouse/partner	48% (443)	50% (186)
Child	41% (373)	41% (151)
Other	11% (105)	9% (34)

The QALY weights of the samples were estimated from the EQ-5D instrument, using weights from the UK [77]. In the follow-up study, EQ-5D was complemented with the EQ-VAS, which uses a RS technique to elicit QALY weights.

The Carers of Older People in Europe (COPE) Index [87] was used to assess the caregiving situation. The COPE Index was chosen because it assesses the caregiver's subjective perception of both the negative and the positive aspects of caring for the older person. It consists of 15 items divided into three scales: negative impact scale, positive value scale, and quality of support scale. The three scales are independent of each other and validated separately. The items included in the three scales [88], used in this paper, are illustrated in Table 3.

Table 3. The sub scales of the COPE Index

The negative impact scale
- Negative effect on emotional well-being - Finding caregiving too demanding - Negative effect on physical health - Difficulties in relationships with family - Feeling trapped in the role of caregiver - Difficulties in relationships with friends - Financial difficulties
The positive value scale
- Finding caregiving worthwile - A good relationship with the cared for person - Feeling appreciated as a caregiver - Coping well as a caregiver
The quality of support scale
- Feeling of support by friends and/or neighbours - Feeling of support by health and social services - Feeling of overall support in the caregiving role - Feeling of support by family

The positive (COPEpos) and negative (COPEneg) scales were used in this paper. Each item is answered with a score of 1 to 4, ranging from "never" to "always". On the COPEneg scale a higher score (maximum 28) indicates a higher degree of negative impact, while on the COPEpos scale a higher score (maximum 16) indicates a stronger influence of positive values.

R-QALY weights (see paper I) were estimated using two different methods. In the first method, a population-based QALY weight was subtracted from the relative's QALY weight (created from the EQ-5D Index, T1), controlling for age and gender. This method is referred to as the "current situation method". The population-based QALY weights used as reference values were obtained from a public health survey conducted in Stockholm county, Sweden in 1998 [89], which measured QALY weights in groups divided by age (10-year intervals) and gender. For example, if a 65-year-old male caregiver has a QALY weight (EQ-5D) of 0.80, and the population-based QALY weight for a 65-year-old man is 0.83, the R-QALY weight would be -0.03.

In the second method used for estimating R-QALY weights, the relatives were compared with themselves. They were asked to reassess their responses to EQ-5D and EQ-VAS hypothetically, assuming that the older person's health was so good that he or she did not need care. By deducting the reassessed QALY weights (for the hypothetical situation) from the previously assessed QALY weights (for the actual situation), the R-QALY weight was found. This method is referred to as the "hypothetical situation method". This process was used with QALY weights created from both EQ-5D and EQ-VAS (from the follow-up study, T2). This method was assumed to be better able to capture wider effects (such as altruistic preferences) in comparison to the current situation method, as the older person's health is assumed to be better.

Several variables that were assumed to be of importance for the R-QALY weights were tested in a regression analysis. These included relatives' age and sex, the possibility of having a break from the caregiving, the number of caregiving hours, the duration of caregiving (in months), and measures of the caregiving situation. Data from the interviews (N=921) and the population-based data [89] (N=2,011) were used in this regression. It was assumed that people included in the population-based data did not provide any informal care, which meant that they were assumed to have 0 caregiving hours, 0 months of duration, no problem in having a break, and the lowest scores on COPEpos and COPEneg.

Statistics

SPSS version 13.0 for Windows was used for the data analysis. Single sample *t*-tests were used to test whether the mean R-QALY weight significantly differed from zero (null hypothesis: mean R-QALY weight = 0). Multiple linear regression was used to examine which variables were able to explain the variation in the QALY weights. In all tests, the significance level was set to $p<0.05$.

Productivity loss

Paper III

The subjects in paper III were drawn from the FRISC II trial [90], which included 3 489 patients admitted to hospital between 1996 and 1998 in Sweden, Denmark and Norway. Patients with chest pain, ST depression or T-wave inversion, and/or elevation of biochemical markers were eligible for inclusion. The patients were randomised to one of four treatments: invasive strategy and long-term dalteparin; invasive strategy and long-term placebo; non-invasive strategy and long-term dalteparin; and non-invasive strategy and long-term placebo.

This paper included only the Swedish patients, as they were the only ones who both answered the EQ-5D instrument and valued their own health state with TTO and RS (EQ-VAS). These instruments were answered by the patients at a total of five occasions; 3 days after admission to the hospital, and at follow up after 3, 6, 12, and 24 months. However, not all of the patients answered the instruments at all five occasions. The valuation procedure was led by an interviewing nurse. In the case of TTO, the nurse asked control questions to make sure that the patient had fully understood the valuation method.

The patients stated their monthly gross income, presented in Swedish Krona (SEK). To further check these incomes, and to clear out potential mistakes between gross and net income, the patients' taxed incomes during the relevant years were controlled before being used in this paper. This method also allowed for the inclusion of income generated from capital. Control of the taxed income was approved by the ethics committee at the Faculty of Health Sciences, Linköping University.

The initial sample consisted of 362 patients from the south-east region of Sweden; as each patient answered the instruments up to 5 times, this generates 362*5=1 810 potential observations. However, only 156 of these patients had stated their own income, decreasing the number of observations to less than half of the potential. The number of observations was further decreased due to the fact that many of the patients had answered the instruments on fewer than five occasions. At the first occasion, 76% of the patients answered, but this rate decreased to 10% at the fifth occasion (after 24 months). The total usable sample therefore consisted of 312 TTO valuations and 309 RS valuations. The mean age among the sample was 65.1 years, and 73% were men.

Statistics

Self-stated income and taxed income were compared using paired samples *t*-tests. The generalised estimation equations (GEE) method was used to test whether the EQ-5D dimensions and income could explain the variation in the valuations of the health states made by TTO and RS. Four models were tested, differing in valuation method and sources of income. GEE is a regression technique based on generalised linear models, and has the ability to handle data with repeated measures [91]. In the context of the present study, this means that the GEE method controls for the potential correlation within individuals caused by each individual having answered the instruments up to five times. The EQ-5D dimensions were included as dummy variables in the GEE tests. TTO values range from 0 – 10, while RS values range from 0 – 100. In all tests, the significance level was set at $p<0.05$. SPSS 14.0 for Windows and SAS 9.1 for Windows were used for the tests.

Paper IV

In paper IV, students at Linköping University in Sweden valued hypothetical health states via a questionnaire which they completed on their own at the end of a class. Some of the students chose not to answer, as they were free to leave if they wished. Participants were randomly assigned into two groups, answering different versions of the questionnaire. The students in the first group (the non-income group) were asked to value the four hypothetical health states; income was not mentioned. The students in the other group (the income group) were asked to value the same health states, but were explicitly asked to consider their expected income in relation to the health states. The students were not informed about the purpose of the study or about the different versions of the questionnaire. The valuation methods included TTO and RS. The time frame used in TTO was 10 years. The questionnaire included four different health states (labelled A – D and presented in Table 4), which were described using the EQ-5D. The health states were chosen to illustrate a variety of health states, some of which may affect income more than others. The health states were also chosen so that comparisons could be made with earlier studies from the UK [77] and Sweden [92]. The order in which the health states appeared in the questionnaire was randomly assigned, in four groups, as it was believed that the students may have changed their thinking about some of the questions after valuing some health states.

Table 4. The hypothetical health states presented for the students

Health state A EQ-5D Index (1, 1, 2, 1, 1)	- I have no problems in walking about - I have no problems with self-care - I have some problems in performing my usual activities - I have no pain or discomfort - I am not anxious or depressed
Health state B EQ-5D Index (1, 1, 1, 2, 2)	- I have no problems in walking about - I have no problems with self-care - I have no problems in performing my usual activities - I have moderate pain or discomfort - I am moderately anxious or depressed
Health state C EQ-5D Index (2, 1, 2, 3, 2)	- I have some problems in walking about - I have no problems with self-care - I have some problems in performing my usual activities - I have extreme pain or discomfort - I am moderately anxious or depressed
Health state D EQ-5D Index (3, 3, 3, 2, 1)	- I am confined to bed - I am unable to wash or dress myself - I am unable to perform my usual activities - I have moderate pain or discomfort - I am not anxious or depressed

Both groups answered a few follow-up questions at the end of the questionnaire; the students in the non-income group were asked whether they had thought of their expected income when they valued the health states, while the students in the income group were instead asked whether the instruction to consider their expected income had affected their valuations. The students in the non-income group were also asked to re-value the health states, this time with explicit instructions to take expected income into consideration, in order that comparisons of the valuations could be made both between the two groups and within the non-income group, before and after explicit instructions to consider expected income. The procedure is described further in Table 5.

Table 5. Description of the procedure used

	Non-income group	**Income group**
Valuation methods:	TTO, RS	TTO, RS
Expected income:	No instruction	Explicit instruction
Follow-up question:	Did you consider income?	Did income affect your valuations?
	↓	
	Re-valuation	
Valuation methods:	TTO, RS	
Expected income:	Explicit instruction	
Follow-up question:	Did income affect your valuations?	

Two hundred students, 54% of whom were women, answered the questionnaires. Their mean age was 23 (range 18–43) years, and 90% were <26 years old. The majority of the students were studying business and administration. The two groups did not differ significantly from each other in any variable. The characteristics of the two groups are presented in Table 6.

Table 6. Characteristics of the subjects

	Non-income group	Income group
N	102	98
Age (mean years):	23	23
	%	%
Sex (women):	50	57
Course		
Business and admin:	55	57
Economics:	19	15
Medicine:	7	14
Logopaedics:	10	8
Physiotherapy:	10	5

Statistics

SPSS version 14.0 for Windows was used for the data analysis. Single-sample *t*-test and Chi-square tests were used to compare the characteristics in the samples. Independent-sample *t*-tests were used to compare the valuations made by the two groups. Paired samples *t*-tests were used to compare the valuations made by the non-income group, before and after explicit instruction of considering income. TTO values range from 0 – 10, while RS values range from 0 – 100. In all tests, the significance level was set to $p<0.05$.

RESULTS

Costs and effects for relatives

Paper I

Paper I highlights the fact that while the relatives of a sick or disabled individual are often affected by this disease or disability, the costs and effects for the relatives are nevertheless generally excluded from CEAs. Although there is a consensus that the cost of informal care should be included to satisfy a societal approach, there is still debate over how to measure and value this.

In this paper, we argue that relatives' costs (informal care) could be measured and valued according to earlier recommendations. That is, by valuing the loss of formal productivity time as the cost of having the person employed, and the loss of informal productivity time as the relative's valuation of this time. Even though most current guidelines include these recommendations, they are generally not followed, and so they should be emphasised more forcefully. We also argue for the inclusion of relatives' effects in the analysis. Relatives' effects are generally not considered at all in health economic evaluations, though they have been discussed in a few papers [13, 24, 44, 93]. Relatives' effects are generated by the decrease in well-being caused by being a relative of an individual with a disease or disability. While this may include effects on relatives' physical health, more commonly it consists of aspects such as mental health, worries and anxiety for the individual. It may also be caused by foregone labour market opportunities [94], which are generally missed in the estimation of informal care. It could also indicate that the relatives have health-related altruistic preferences for the disabled or sick individual, meaning that relatives value the individual's health even if the relatives themselves are not affected by the individual's health state [28, 95]. Relatives' effects may occur even for relatives who do not provide informal care, and are therefore not identical to the sum of positive and negative aspects of providing informal care. The members of a family are, for example, often negatively affected by one member's disease or disability, even if none of them are providing informal care.

The results of paper I show that relatives' effects are not included within an individual's QALY-estimation, and so must be specifically included in the analysis. This is the case regardless of whether welfare economics or extra-welfarism is chosen as the theoretical basis for the analysis, since an extra-welfaristic approach generally tries to maximise the health outcome, and so should also include relatives' health outcomes.

The outcome measure used for relatives' effects should preferably represent the relatives' preferences for the individual's health. In this paper, we introduce a new measure, R-QALY weights, to use for relatives' QALY weights. R-QALY is defined as the effect on QALY caused by being a relative of an individual with a disease or disability. The R-QALY weight is negative if the relative's QALY weight is negatively affected by the disabled or sick individual, zero if no effect exists, and positive if there is a positive effect. When R-QALYs are used in the analysis, however, lost leisure time due to informal care should not be captured in the cost estimation of informal care, as this is included in the R-QALY weight.

Paper I also discusses methods for studying relatives' effects (R-QALYs). The methods used for finding individuals' QALY weights, such as TTO, SG or RS, could also be used to estimate the R-QALY weights; however, adjustments must be made in order to capture the effects on the relatives rather than the cared-for individual. Indirect methods using generic instruments such as the EQ-5D are also possible, and would simplify the inclusion of relatives' effects in the analysis. However, generic health-related QoL instruments will not be able to capture all aspects of relatives' effects, such as altruistic preferences. Specific relative-related instruments could be used - where the CarerQol instrument [96] is promising - but this complicates the inclusion of relatives' effects in the analysis.

Paper II

In paper II, we investigated whether the EQ-5D instrument could be used to find R-QALY weights, using two different methods, in a sample of relatives providing care or support to an older person. Negative R-QALY weights could be found by both methods, but they were stronger when the hypothetical situation method was used rather than the current situation method (see Table 7). Furthermore, within the hypothetical situation method, the R-QALY weights were more negative when using the RS (EQ-VAS) rather than the EQ-5D Index.

Table 7. Relatives' mean R-QALY weights

Method	Instrument	N	Mean R-QALY	Sig.
Current situation method	EQ-5D	894	-0.015	0.041*
Hypothetical situation method	EQ-5D	329	-0.062	<0.001*
Hypothetical situation method	EQ-VAS	334	-0.099	<0.001*

* = significant; $p<0.05$

Relatives' age and sex and the COPEneg and COPEpos scales were significant in explaining the variation of the QALY weights (see Table 8). Furthermore, the impossibility of having a break and the duration of caregiving both affected the QALY weight negatively. Difficulty in having a break and the number of caregiving hours per week could not explain the variation in the QALY weights. All the variables included in the model explained 17.5% of the variance in the QALY weight. The negative scale of the COPE Index had a larger effect on the QALY weight than did the positive one.

Table 8. Variables explaining the variation in the QALY weights

	Coefficients		P-value
	B	Std. Error	
(Constant)	1.049	0.015	<0.001*
Relative's age	-0.002	<0.001	<0.001*
Relative's sex (women)	-0.024	0.004	<0.001*
COPEneg	-0.013	0.001	<0.001*
COPEpos	0.007	0.001	<0.001*
Difficult to have a break	-0.006	0.009	0.534
Impossible to have a break	-0.044	0.010	<0.001*
Number of caring hours	<-0.001	<0.001	0.200
Duration of caregiving	<-0.001	<0.001	0.019*

$R=0.418$, R square=0.175, Adj R Square=0.172 * = significant; $p<0.05$

Productivity loss

The other area of interest in this thesis concerns the potential relationship between individuals' incomes and valuation of health states. This relationship is important, as it may reveal how productivity loss caused by morbidity should be included in the CEA. Papers III and IV were aimed at investigating whether income is included in the health state valuations. In the first of these, we discuss the potential relationship between income and the valuation of health states, and test whether individuals' incomes can explain their valuations of their own health state. In the second, we test whether explicit instructions to consider expected income in hypothetical health states affect the valuations.

Paper III

This study showed that productivity loss could affect the valuation of health states if the valuation methods are affected by income. Whether this is so depends on the outcome measure that is chosen and the valuation method that is used.

The empirical tests used data from patients in the FRISC-II trial, including both self-stated income and controlled taxed income. The two sources of income did not differ significantly from each other (see Table 9). For some patients, however, the self-stated and the taxed income differed. The most likely reason for this is that some of the patients stated their net income instead of their gross income, but it is also possible that some patients included grants in their self-stated incomes. About 57% of the patients had income generated from capital, with the taxed income including income from capital being higher than the self-stated income.

Table 9. Self-stated monthly income, taxed monthly income and monthly income generated by capital (SEK)

	N	Mean	Min.	Max.	SD
Self-stated income	312	12 585	2 500	35 000	5 221
Taxed income	301	13 036	3 117	37 850	5 203
Capital income	306	1 275	0	58 840	5 267
Taxed income + capital	301	14 331	3 186	71 132	7 403

	***t*-test for equality of means**		
	Mean diff.	SE diff.	P-value (two-tailed)
Self-stated income compared with taxed income	451	421	0.285
Self-stated income compared with taxed income + capital	1746	516	<0.01*

* = significant; p<0.05

The percentages of answers in the five dimensions of EQ-5D are presented in Table 10. Only a few (<5%) of the patients had any problems within the self-care dimension, while a majority of the patients had problems in the pain/discomfort dimension.

Table 10. Percentages of answers in the five dimensions of EQ-5D (N=312)

	No problem	Moderate problems	Severe problems
Mobility	70.5	28.2	1.3
Self-care	95.2	3.5	1.3
Usual activities	57.7	31.1	11.2
Pain/discomfort	21.8	70.8	7.4
Anxiety/depression	52.2	46.5	1.3

The valuations made by EQ-5D Index, TTO, and RS are presented in Table 11. The different valuation methods elicited values that were well in accordance with each other.

Table 11. QALY weights estimates

	N	Mean	Min.	Max.	SD
EQ-5D Index	312	0.68	-0.09	1	0.25
TTO	312	0.71	0.10	1	0.20
RS	309	0.66	0.05	1	0.18

An analysis of GEE parameter estimates, including the EQ-5D dimensions and income as independent variables and the health state values (elicited by TTO and RS) as dependent variables, showed that income in most cases could not explain the variation in the values (see Table 12). Self-stated income was, however, a significant variable in explaining the values made by RS; the QALY weight increased by 0.03 when self-stated income increased by 1.000 SEK.

Table 12. Analysis of generalised estimation equation parameter estimates of EQ-5D dimensions and income

Dependent variable	**TTO,** N=312			**RS,** N=309			**TTO,** N=312			**RS,** N=309		
	B	Z	Sig.	B	Z	Sig.	B	Z	Sig.	B	Z	Sig.
Constant	0.78	22.68	<0.01*	0.75	27.02	<0.01*	0.81	26.36	<0.01*	0.79	31.60	<0.01*
Mobility												
- moderate problems	-0.05	-2.04	0.04*	-0.07	-3.65	<0.01*	-0.05	-2.07	0.04*	-0.08	-3.74	<0.01*
- severe problems	-0.10	-0.91	0.36	0.06	0.73	0.46	-0.10	-0.93	0.35	0.06	0.81	0.42
Self-care												
- moderate problems	-0.04	-0.92	0.36	-0.09	-2.04	0.04*	-0.04	-1.00	0.32	-0.09	-2.17	0.03*
- severe problems	-0.02	-0.26	0.79	-0.02	-0.19	0.85	-0.02	-0.24	0.81	-0.01	-0.18	0.86
Usual activities												
- moderate problems	-0.06	-2.58	0.01*	-0.08	-3.62	<0.01*	-0.06	-2.52	0.01*	-0.08	-3.47	<0.01*
- severe problems	-0.15	-3.79	<0.01*	-0.17	-5.45	<0.01*	-0.15	-3.77	<0.01*	-0.17	-5.36	<0.01*
Pain/discomfort												
- moderate problems	-0.04	-1.61	0.11	-0.05	-2.51	0.01*	-0.04	-1.62	0.11	-0.05	-2.51	0.01*
- severe problems	-0.06	-1.21	0.23	-0.13	-3.26	<0.01*	-0,07	-1.27	0.20	-0.14	-3.37	<0.01*
Anxiety/depression												
- moderate problems	-0.02	-0.87	0.38	-0.05	-3.08	<0.01*	-0.02	-0.91	0.36	-0.05	-3.19	<0.01*
- severe problems	-0.20	-2.24	0.03*	-0.21	-6.12	<0.01*	-0.20	-2.19	0.03*	-0.21	-6.01	<0.01*
Self-stated income	0.002	0.91	0.36	0.003	2.36	0.02*						
Taxed income							<0.01	0.07	0.94	<0.01	0.66	0.51

* = significant; p<0.05

Paper IV

The results of paper IV showed that the majority did not consider their expected income when they valued hypothetical health states if income was not specifically asked for. Among the students in the non-income group, 96% stated in response to the follow-up question of the questionnaire that they had not thought about their expected income when they valued the health states. In the income group, 40% felt that thinking about their expected income had affected their valuations of the health states. The most common explanation for how income affected the valuations was that a lower expected income may lead to a decreased QoL, resulting in lower values.

The mean values for the health states for both groups are presented in Table 13, together with comparisons of the mean valuations. Health state A generated the highest mean value, and the other health states received lower values, with a gradual decrease from the highest to the lowest value, as expected from earlier studies. For state A, the groups differed in their valuations made using the TTO method. For states C and D, the groups differed in their valuations made using the RS method. State B, which was the only health state not to show significant differences between the two groups, was also the only health state that did not include problems within the dimension of "usual activities". The health state showing the largest differences between the RS valuations of the two groups was state D, the only health state in which the students were assumed to be completely unable to perform their usual activities.

Table 13. Mean valuations of the health states and independent-sample *t*-tests for equality of means between the non-income group and the income group

Health state	Method, group	N	Mean	SD	t-test for equality of means		
					Mean diff.	S.E. diff.	Sig. (2-tailed)
A (1,1,2,1,1)	TTO, non-income group	100	8.2	1.82	0.61	0.26	0.02*
	TTO, income group	97	7.5	1.88			
	RS, non-income group	89	76	15.8	3.55	2.45	0.15
	RS, income group	89	72	17.0			
B (1,1,1,2,2)	TTO, non-income group	99	7.2	1.81	0.03	0.26	0.91
	TTO, income group	94	7.2	1.75			
	RS, non-income group	89	67	17.4	-2.67	2.46	0.28
	RS, income group	89	70	15.4			
C (2,1,2,3,2)	TTO, non-income group	99	4.8	2.42	0.28	0.34	0.41
	TTO, income group	93	4.5	2.26			
	RS, non-income group	89	45	19.5	6.29	3.04	0.04*
	RS, income group	87	39	20.7			
D (3,3,3,2,1)	TTO, non-income group	100	3.9	2.63	0.59	0.36	0.10
	TTO, income group	92	3.3	2.29			
	RS, non-income group	89	33	20.6	7.94	2.94	0.01*
	RS, income group	88	26	18.5			

* = significant; $p<0.05$

The students' responses with regard to mean expected incomes in the different health states are presented in Table 14, as a percentage of the specified income at full health. For example, if the specified income at full health was SEK 25,000 and the student expected an income of SEK 20,000 in health state A, this is calculated as 80%. Although health state A was valued preferentially over the other health states, it had a larger effect on expected income than did health state B. The expected incomes in health states C and D were less than half of the specified maximal income.

Table 14. Effects on expected income caused by hypothetical health states

Health state	Percentage of the income at full health	SD
A	73%	0.18
B	82%	0.17
C	47%	0.21
D	30%	0.20

Table 15 presents a comparison of the valuations made by the non-income group, before and after explicit instructions to take expected income into consideration. This group was the one that first valued the health states with no instructions to consider income, and afterwards valued the health states again, this time with the explicit instruction to consider their expected income. The differences between the means were similar to those between the non-income group and the income group. However, more of the differences were significant, such as the RS value of health state A and the TTO value of health state D.

Table 15. Mean valuations of the health states and paired-sample *t*-tests for equality of means between valuations made before and after explicit instructions to consider income, in the non-income group

Health state	Method	N	Mean	SD	Paired samples *t*-test Mean diff.	S.E. diff.	Sig. (2-tailed)
A (1,1,2,1,1)	TTO, before income instruction	100	8.2	1.82	0.46	0.16	<0.01*
	TTO, after income instruction	93	7.6	1.99			
	RS, before income instruction	89	76	15.8	7.92	1.95	<0.01*
	RS, after income instruction	84	67	20.0			
B (1,1,1,2,2)	TTO, before income instruction	99	7.2	1.81	-0.11	0.14	0.44
	TTO, after income instruction	94	7.3	1.78			
	RS, before income instruction	89	67	17.4	1.04	1.21	0.39
	RS, after income instruction	84	66	17.4			
C (2,1,2,3,2)	TTO, before income instruction	99	4.8	2.41	0.11	0.18	0.56
	TTO, after income instruction	95	4.7	2.36			
	RS, before income instruction	89	45	19.5	4.11	2.01	0.04*
	RS, after income instruction	84	40	19.1			
D (3,3,3,2,1)	TTO, before income instruction	100	3.9	2.63	0.45	0.13	<0.01*
	TTO, after income instruction	94	3.3	2.56			
	RS, before income instruction	89	33	20.6	6.16	1.41	<0.01*
	RS, after income instruction	84	26	17.7			

* = significant; $p<0.05$

DISCUSSION

Cost-effectiveness analyses rarely, or perhaps never, fulfil the common recommendation of using a societal perspective, being based in welfare economics. A CEA can potentially be based on welfare economics, but this depends on the costs and outcome measure included in the analysis. The outcome measure should represent individuals' preferences for the different possible health states; a common strategy is to use QALYs, which under certain assumptions represent individuals' utilities from health [67]. However, it has been shown in practice that the elicitation of QALY weights does not satisfy these assumptions, and a QALY is not in itself a utility [68]. Therefore, it is not clear that using the CEA with QALYs as outcome measure will guide the decision maker to the societal most optimal decision.

As there is no other well-accepted and preferable method available, there is a need to develop the methods used for CEA. The debate regarding the analysis mostly concerns what is included in QALY, which in turn influences the costs that should be included. The papers included in this thesis make it clear that neither relatives' full costs and effects, nor the productivity loss generated by disease or disability, are usually included in QALYs. To remain consistent with the societal perspective, these areas should be included in the CEA and therefore need to be included separately.

The QALY weight represents individuals' preferences for health states described in terms of health-related QoL. Aspects that are not covered within individuals' health-related QoL will therefore not be included in the QALY weight. It has earlier been suggested that a "super-QALY" could be used [97], including various aspects which are complementary to the "normal" QALY, for example the effects occurring from acute conditions, non-linearity over time, and so on [98]. Such a "super-QALY" could also be complemented by relatives' effects and possibly also by individuals' productivity loss. Whether this is desirable though is not obvious. Decision makers may prefer a "simple QALY" that only includes individual's health effects, and to have all other effects presented outside the analysis.

Costs and effects for relatives

Papers I and II of this thesis show that the relatives of an individual are often affected by that individual's disease or disability. The relatives may provide informal care, and the cost of this informal care should be included in the analysis. They may also incur effects on their own well-being, whether they provide informal care or not. There are interpersonal linkages in individuals' utility functions [10], and the analysis should capture these spill-over effects. The costs and effects for the relatives are nevertheless often excluded from CEAs. This exclusion of relatives' costs and effects is not usually based on theoretical arguments, but rather on reasons such as tradition, comparability with earlier analyses, valuation problems, and the assumption that relatives' costs and effects do not matter. In general, it seems that relatives' costs and effects are not actively excluded from the analysis, but rather forgotten. It is important to discuss these issues, and to develop the valuation methods to allow visualisation of the importance of relatives' costs and effects.

The estimation of relatives' costs has not been in focus in this thesis, as this has been studied in several earlier papers. The idea of using the human capital approach to estimate the value of informal care is accepted as the most correct method of estimating these costs. Instead, we have focused on relatives' effects, and suggested the use of a new measure, R-QALYs, both to visualise relatives' effects and to include them in the analysis. The R-QALY weight should represent relatives' preferences for the individual's health state, and include health-related aspects as well as altruistic preferences and forgone possibilities caused by the individual's disease or disability.

There are a number of possible ways to estimate R-QALY weights. The same methods that are used to estimate individuals' QALY-weights could also be used for the R-QALY weights. However, there are several complicated aspects involved in asking the relatives questions such as how many years they would trade for an improvement in the individual's health. Hence, before these methods can be used to estimate valid R-QALY weights, they will need to be researched further. The easiest method to use is probably the RS technique, in which relatives mark their relative-related QoL on a scale. Transformation of the relative-related QoL to a scale anchored with death at one end and full health at the other is then needed to generate R-QALY weights.

Indirect methods could also be used for finding R-QALY weights, but this requires instruments that are capable of assessing relatives' effects. Instruments specifically designed for this task do exist, but only a few of them are such that the results are compatible with the methods used in CEA. We are aware of three such instruments [96, 99, 100], but none of them has been widely used. The most recently developed one, and also the most comprehensive, is the CarerQol Instrument (care-related quality of life) [96]. Further studies and use of this instrument could allow the elicitation of R-QALY weights for the states constructed by the instrument. There are also generic instruments that could be used to value relatives' effects. One example is the generic instrument EQ-5D. There is, however, unclear whether EQ-5D is suitable for measuring relatives' effects as it measures health-related QoL. As shown in paper II, EQ-5D can capture some of the relatives' effects, but there are probably other attributes that are more important for the relatives, such as altruistic preferences, financial situation, coping capacity, and so on. The main advantage of using the same generic instrument for both individuals and their relatives is that their QALY weights can easily be combined.

Relatives' costs are best valued in monetary terms, and this is also a promising method for relatives' effects. In this case, R-QALY weights are not needed. Mulvaney-Day [52] used the CV method among relatives of individuals with mental illness, focusing on relatives' WTP for a medication that would cure the individual completely. With this method, the value would include both relatives' costs and their effects. Another attempt was made by van den Berg et al. [49], who used the CA method. They let informal caregivers chose between situations where some attributes differed; the amount of hours provided for informal care, informal care tasks, and monetary compensation. This method could therefore be used for estimates of both relatives' costs and effects. The well-being valuation method has also showed some capacity for capturing relatives' effects [56, 57]. All these monetary valuation methods are potentially suitable to use for estimating relatives' costs and effects, but they are all in need of more research. To use a monetary value of all relatives' costs and effects could be seen as an advantage as this would enable the analysis to only have the individual's effects in the denominator. However, valuing relatives' effects in monetary terms may threaten the political and public acceptance of using health economic analyses for decisions in health care.

If relatives' costs and effects are measured and combined with the individual's costs and effects in the analysis, there is a risk of double counting. There are at least two major sources of double counting related to relatives' costs and effects. First, if the individual has already included the relatives' effects in their own valuations, the separate inclusion of relatives' effects would lead to double counting. However, this may not actually be a problem in practice. It could be argued that this is not really double counting, as it is the indirect effect on the individual that is captured, being part of the total spill-over; the direct effect on relatives is not captured within the individual's health state valuation. Double counting only occurs if the individual is not affected by the effects on his or relatives, but includes them anyway. Another risk for double counting occurs if relatives' effects include aspects that are also captured in the estimation of relatives' costs. This is more complicated to avoid. For example, if relatives reduce their hours of paid work in order to provide informal care, this productivity loss will be included in the cost of informal care. If the same productivity loss furthermore leads to reduced well-being, this may be captured when relatives' effects are measured. The relatives' productivity loss will therefore be counted twice if both the cost of informal care and relatives' effects are included in the analysis. However, it has been shown that the methods to elicit QALY weights do not include income, and this may also be the case for R-QALY weights. Another example of this double counting would be if the cost of lost leisure time is included in the estimation of informal care and the same lost leisure time is captured in relatives' effects. As the lost leisure time is included in the R-QALY weight, this should not be included in the cost of informal care in order to avoid double counting.

A summary of costs and effects for the disabled or sick individual and his or her relatives is given in Table 16, together with methods of valuations and some areas where further research is needed. In this table, the focus is on relatives' costs and effects, and the challenges that come with including them in a CEA. Relatives' effects could either be estimated in monetary terms and be included in the numerator of the CEA, or be calculated in terms of 'effects' and be included in the denominator.

Table 16. Costs and effects for individuals and relatives in a cost-effectiveness analysis

	Individual	**Relatives**
Costs		
What kind of costs	Direct costs Indirect costs Future costs?	Cost of informal care (incl. direct and indirect costs) Other costs
Methods for valuation	Opportunity cost method Shadow price	Opportunity cost method Shadow price Contingent valuation method Conjoint analysis method
Difficulties / further research	-	Valuation of lost leisure time Avoiding joint production
Effects		
What kind of effects	QALY Life years Other outcomes	R-QALY QoL Monetary values
Methods for valuation	Direct methods Indirect methods	Direct methods Indirect methods Contingent valuation method Conjoint analysis method
Difficulties / further research	-	Outcome measure Valuation methods Incorporating effects in the CEA Avoiding double counting

- = Not in focus of this thesis

Productivity loss

In papers III and IV, the relationship between income and the elicitation of QALY weights was studied theoretically and also tested empirically. We found that income does affect the QALY weights if individuals include the utility generated by consumption within their QALY weights. The empirical tests, however, showed that a majority of individuals do not consider their income when they value health states by TTO or RS (even though RS was shown to have a greater ability than TTO to capture income). The explicit instruction to consider income affected those health states that were assumed to have consequences on the ability to perform daily activities. These findings therefore give support for including productivity costs caused by morbidity in the analysis, as these costs are not, or are only to a minor extent, incorporated in the individuals' QALY weights when TTO or RS is used to value the health states.

The relationship between income and QALY depends on the method that is used to elicit the QALY weights. QALY weights are often assumed to represent the utility of the individual's health related QoL, rather than their general utility. Health-related QoL focuses on the individual's subjective assessment of how disease and interventions affect their health state [65]. Therefore, depending on what the QALY weight is assumed to represent, the issue concerning income may differ. Furthermore, some methods of eliciting QALY weights may be more affected by income than others. Direct methods often value "your current health state", while indirect methods describe health states in more restricted terms (for example in terms of disability and distress). Sculpher and O'Brien argue that income can theoretically also affect indirect methods [101], both when the health state is found and in the valuation process. There are also differences between the direct methods which may affect the relationship between income and QALY. For example, with the TTO the individual is asked to choose between living a certain number of years in their own current health state, and living a reduced number of years in perfect health. In this case, the individual's preferences for the health states are revealed, including all aspects they assume relevant. The health states are also supposed to last for several years, which may make the individual consider their income to a higher extent than if the length of time had not been mentioned. The RS, on the other hand, uses a VAS that has well-defined endpoints, generally ranging from worst imaginable health to best imaginable health. Income is not mentioned, and so in theory should not affect the valuation. Furthermore, the valuation by RS is made at a single point in time, rather than within a time-frame, which may lead to less consideration of how income is affected by the health state. These theoretical differences concerning how income should be considered in TTO and RS were, however, not apparent in the empirical findings. The reason may be that TTO is a more complex technique and it might therefore be more complicated for individuals to assume aspects that are not directly mentioned in the valuation question.

Donaldson et al. [63] have provided an analytical framework in which non-monetary valuation methods are shown theoretically to be affected by income. They identified several reasons why income may be captured in non-monetary valuation of health states (such as QALYs); income-based differences in life expectancy, income-based differences in the marginal utility of life years, and non-income-based differences in the marginal utility of life years. Gerdtham and Johannesson [62] have furthermore shown that QALY is affected by income-based differences in life expectancies. As life expectancy is income related, poorer individuals have less time to trade for QoL improvements. Donaldson et al. [63] therefore conclude that no economic evaluation can be "income-free", and that the process of valuation reflects the characteristics of the population providing the valuation.

Even though income may have some effect on the health state valuations, this is not equal to the societal cost due to an individual's productivity loss. The reason is that the existence of insurance and compensating systems in the society leads to reduced income loss for the individual [64]. In order to capture the societal cost, it would be preferable to include the productivity loss as a cost within the analysis, rather than as a decreased effect. To make sure no income effects are captured in the QALY weight, the Canadian guidelines recommend that the individual should be told that all potential income loss will be fully reimbursed when the QALY weights are elicited [5]. This approach, however, may make the individuals think of income implicitly. The empirical tests in paper III showed partially different results when self-stated or taxed income was used as the explanatory variable; self-stated income had a larger ability than taxed income to affect the valuation made by RS. This could be a sign that individuals' subjective perceptions of their incomes differ from their actual taxed incomes (and the two income measures may furthermore differ due to factors such as grants and insurance). Therefore, even if explicit instructions are given to consider income, it is unlikely that this would be equal to the societal productivity loss.

The results of the papers can be compared with some other studies. Krol et al. [102] found that VAS valuations of health states made by respondents from the general public did not differ significantly between two groups, one of which was explicitly asked to consider income effects, and the other of which was asked not to consider income effects. They furthermore found that in the absence of instruction to consider the effect of ill health on income and leisure time, 36% included these effects in the VAS valuations. In another study, Krol et al. [103] tested TTO valuations in a similar way, and found that 64% of the respondents spontaneously included income effects. They also showed that for the worst health state presented, explicit instruction of considering income gave lower TTO valuations compared to the group with no instruction of considering income. Richardson et al. [104] found that most respondents assumed an unchanged consumption level when valuing health states. Myers et al. [105] investigated whether undergraduate students automatically considered morbidity costs in their health state valuations made by SG. They found that students who were informed about the morbidity costs valued the health states lower than students who were not informed of these costs. Sendi & Brouwer [106] found that when income effects were not asked for, a majority of respondents did not take them into consideration when valuing health states by VAS. Meltzer et al. [107] studied whether people with blindness or severe back pain considered financial effects in their TTO values of their own current health states, and found that the majority did not consider them, even when financial effects were specifically mentioned. The results from all these studies go in the same direction as the results from papers III and IV. However, in the studies by Krol et al. [102, 103], a much higher percentage of individuals implicitly considered income effects (compared to the findings in paper IV), though not resulting in differences in mean valuations.

The finding that income is not considered in the QALY weight can be used as a reason to exclude CAL from the analysis. This follows the consistency criterion, based on Nyman's argument [38]. However, even though income is not captured in the QALY weight, it probably does not mean that no consumption is expected when individuals value health states. It could rather mean that consumption is not thought of, and is therefore considered to be maintained on a similar level as before. In this case, the same consistency criterion argument could be used to motivate the inclusion of CAL in the analysis. If CAL is excluded, only the costs of reaching a certain health state has been included, and not the costs of staying in that health state. Several recent studies have argued that the consistency criterion means that CAL should be included in the analysis [39, 40, 108]. However, it is still unclear what the QALY weight actually includes; and Liljas et al. [60] therefore argue that it seems premature to include CAL. Recently published theoretical papers argue both in favour of [39, 109] and against [36] the inclusion of CAL, depending on the view of the internal consistency argument and on what perspective the analysis uses.

The question of whether CAL should be included or excluded goes deeper than the debate regarding if the utility of consumption is captured in the QALY weight. In general, it depends on both the theoretical framework that is used for the analysis and the purpose of performing the analysis. From a societal perspective, using welfare economics, the inclusion of CAL seems accurate. The argument for excluding CAL are rather based on either the use of a decision-makers perspective or due to the incompleteness of the methods used for valuing health states in a CEA.

Implications for analysts

The findings of this thesis have some implications for the CEA. In the QALY weights that are estimated from a medical treatment, neither individual's relatives nor income are included. These dimensions must therefore be included separately in the analysis. The two fields studied within this thesis are closely related to each other, as the cost of informal care mainly constitutes of productivity loss (including loss of leisure time). They also both depend on what is included in the QALY weight.

It is sometimes argued that welfare economics is not a suitable theoretical base for decisions in health care, as health differs from most other commodities [110]. For example, health cannot be easily exchanged for money, cannot be bought or sold, and cannot be kept in a safe place and be used later. Therefore an alternative to welfare economics, known as extra-welfarism, has often been advocated. This approach was built on studies of basic capabilities by Sen [111], and further developed by Culyer to be used in health economic evaluations [110, 112]. The extra-welfaristic approach, used within cost-effectiveness analyses, requires health interventions to be analysed according to their impact on health rather than the utility they bring. There is debate over which approach should be used [113, 114], and this may have caused misunderstandings about the need for including relatives' costs and effects. However, the underlying approach used for the analysis has little relevance for the issues studied within this thesis. Relatives' costs and effects are relevant in both welfare economics and extra-welfarism, and the productivity loss caused by morbidity should be included if a societal perspective is chosen, no matter which theory that is used. What might differ is what is the aspects that are assumed to be included in QALY, as welfare economics assumes that

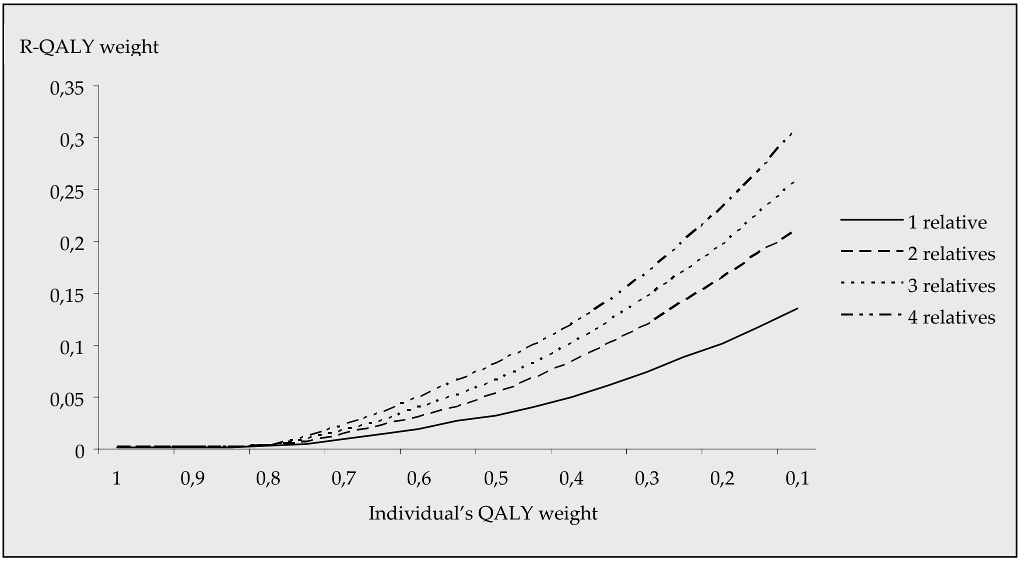
QALY represents individual's preferences for health while extra-welfarism rather interprets QALY as a measure of health [115].

Because CEAs are used for decision making, it is important to find ways of incorporating all relatives' costs and effects within the analysis. Hardly any CEAs performed to date have discussed or included relatives' effects. The US panel on cost-effectiveness in health and medicine [34] mentioned in 1996 that the analysis should include effects of "significant others" in order to fulfil a societal approach. The importance of this has also been stressed by some other studies that discussed the possibility of including informal caregivers' health effects in the analysis [46, 47, 116]. To include parents in analyses of interventions in children is also a subject that has been discussed [117].

If a monetary value of relatives' effects is sought, the CV method, the CA method or the well-being valuation method could be used. However, to assess the effects in monetary units is not without objection. In the first place, it is difficult to find such a value. There are methodological difficulties regarding how the questions should be worded so that relatives' real preferences appear. It has been shown that WTP studies often overestimate the true societal value [118]. Secondly, it could be hard to argue that a method which is not accepted for valuing individual's effects should be used to value relatives' effects. The suggested method of using R-QALY weights instead of a monetary value has the potential to capture these effects, but it does not clearly enable a combination with the individuals' QALY weights. Several authors [47, 119, 120] have stressed that the QALY weights of the disabled or sick individual and those of their relatives are not of the same type, and therefore cannot be combined. One is generally health-related, and the other may be care-related or relative-related. When the two kinds of QALY weights are determined using different methods, the direct combination of the weights is problematic and some kind of transformation of the weights is needed. However, this is not impossible. Aggregation of utilities in order to represent societal preferences is commonly used in decision making even though it has been shown to be theoretically troublesome [121]. If the same method is used to value the effects, then the combination of the individual's and the relatives' effects is no more complicated than combining the effects from different individuals.

If relatives' effects should be incorporated in the analysis, this must be done in a feasible way. It would be very resource consuming to study relatives' effects every time a medical technology is assessed, and it may also be difficult to identify all the relatives. Following the idea of using R-QALYs, one solution may be to use pre-defined templates in the form of R-QALY weights that can be used in different situations. This could also be used by the decision makers when they know that relatives' effects are of importance but not incorporated in the analysis. An example of how these templates could look is given in Figure 4. Depending on the severity of the individual's disease or disability, and the number of relatives, R-QALY weights differ. In this example it is assumed that the R-QALY weights are exponentially affected by the severity of the disease or disability. In addition it is assumed that the more relatives, the stronger the R-QALY weight. The real values of these effects are nevertheless not known, and the values included in the figure are only meant as examples. A similar template could be used if relatives' effects are presented in monetary values.

Figure 4. Example of relatives' R-QALY weights



The papers included in this thesis, as well other studies of this issue, show that an individual's income does not affect their QALY weights to any great extent. Even if the QALY weights were affected by income, this would not represent the true societal productivity loss, due to factors such as insurance and taxes. It is therefore recommended that the societal productivity loss is calculated as a cost, and that efforts are made to avoid including income effects in the health state valuation (the QALY weight). However, lost leisure time should not be included in the estimation of productivity loss, as it is included in the QALY weight. As it is preferable that QALY weights are not affected by income, the TTO is a preferable method to use, rather than the RS. This is because RS seems to have a higher ability to capture individuals' income than TTO. This is contrary to the theoretical arguments, where RS is supposed to have less ability to capture income than TTO.

As different analyses are commonly compared with each other, it is of great importance that the analyses are carried out in the same way. If some analyses include the productivity loss among the costs, while others assume that this is included in QALY, this could heavily bias the analyses so that they are not comparable. Furthermore, if some of the analyses include relatives' costs and effects and others do not, their results are not entirely comparable. This means that it could currently be justified to ignore the relatives in the main consequences, and instead to perform the analyses required by standard methods and then include relatives' costs and effects in sensitivity analyses. Many guidelines point out, however, that all costs and effects, including those for relatives, should be included. If these recommendations are promoted more vehemently, and guidance is given on how relatives' costs and effects can be included, it is likely that more analysts will begin to consider it. Even then, it might be reasonable to present the results both with and without relatives' costs and effects, to enable comparisons.

Ethical considerations

If relatives are affected by an individual's disease or disability, this will affect the total utility. It could therefore be considered unethical to exclude relatives from the analysis, because it would mean that relatives' utilities are not counted, and that decisions are taken that may not be optimal for society. However, the inclusion of relatives' costs and effects can cause other ethical implications. For example, individuals with many relatives may gain a higher efficacy from the treatment, and this could lead to that individuals with many relatives (family members and friends) being given higher priority than individuals with fewer relatives, even though their conditions are identical. On the other hand, health economics analyses do not compare treatments for specific individuals; the comparisons are always made on a group level. A patient group has an equal number of relatives, and including relatives' costs and effects would improve the cost-effectiveness of the most effective treatment. For policy decisions, therefore, relatives' costs and effects are of importance only for assessing whether a medical intervention is cost-effective, and should not be used for prioritising between different individual patients. However, if the same threshold value for the acceptance of a QALY is used for all medical interventions, this could in the long run lead to that patient groups with many relatives are prioritised before patient groups with fewer relatives.

The question concerning individuals' productivity loss also raises ethical questions. Use of the human capital approach could lead to improved ICERs for treating individuals with high salaries compared to individuals with lower salaries, all else being equal. Furthermore, treatments for individuals who are still productive on the market may be prioritised over treatments for retired individuals, based on the treatments' ICERs. However, the productivity loss should certainly be included in the CEA somewhere, and question of whether this is in the numerator or in the denominator of the CEA is not an ethical issue but rather an empirical one. There have also been claims that the costs of productivity loss should not be included in the analysis at all, as they do not affect the health care budget and may lead to discrimination of against those who are not in the labour market [122, 123]. The proponents of this view argue that the issue of including production loss is not merely a technical problem (in order to avoid double counting) but rather a normative issue, whose solution depends on the value judgements on which the analysis is based. This argument, however, is not supported in welfare economics.

Concluding remark

Very few individuals live in isolation, without family or friends, and there are often spill-over effects within these groups. For a CEA to satisfy the societal approach, it cannot be restricted to studying only the individual who undergoes a medical treatment. Relatives may receive utility from each other's incomes, and also from each other's health states. If relatives' costs and effects and the cost of individuals' productivity loss are missed for treatments where they are assumed to be of significant importance, the result of the analysis will only be partial. The decision makers may therefore not receive full information, which could lead to decisions that are not optimal for society. It is important that the analyses are presented in such a way that the decision maker can determine what is included in the analysis and what is not.

CONCLUSIONS

- Neither relatives' costs and effects, nor individuals' productivity loss caused by morbidity, are captured in QALY weights elicited by TTO or RS.

- Relatives' costs and effects should be included in a CEA from a societal perspective, which is generally not the case today. The new measure, R-QALY, is one way to visualise relatives' effects and also as a method of including this in the analysis. More studies on relatives' effects are needed, as little is known about what these effects consist of and how they should be estimated and included in the analysis.

- Relatives' effects can be found using the EQ-5D instrument, but this probably only captures a minor part of their effects. The EQ-5D does not capture altruistic preferences, and probably only captures parts of the relatives' worries and foregone opportunities.

- Productivity loss caused by morbidity or mortality should be included in all analyses which take a societal approach. The cost of this loss should preferably be included in the numerator of the CEA.

- The utility of changed consumption level is not captured in the QALY weights, which is one argument for the exclusion of CAL from the CEA. However, as a basic consumption level is included in QALY, there are nevertheless reasons to include CAL in the analysis.

SUMMARY IN SWEDISH - SAMMANFATTNING PÅ SVENSKA

Hälsoekonomiska analyser används ofta som underlag för beslut inom hälso- och sjukvården. Det finns dock metodologiska och empiriska områden inom dessa analyser där det råder osäkerhet idag. Två områden där mer forskning behövs har studerats i den här avhandlingen. Syftet med avhandlingen var att få ökad kunskap om vad som borde inkluderas i en kostnadseffektivitets-analys ur ett samhälleligt perspektiv. Detta inkluderar studier avseende närståendes kostnader och effekter, samt studier avseende värdering av individers produktionsbortfall till följd av sjukdom. De delstudier som avhandlingen baseras på har undersökt teoretiska aspekter av de ovan nämnda områdena samt testat sambanden empiriskt. Tre olika datamaterial har använts. Kostnadseffektivitetsanalysen och skattningen av kostnader och effekter är centrala delar i samtliga delstudier. Det effektmått som i huvudsak används är kvalitetsjusterade levnadsår (QALYs).

Närstående till en individ med en sjukdom eller funktionsnedsättning ger ofta informell vård och de får dessutom ofta en påverkan på sin livskvalitet till följd av individens sjukdom eller funktionsnedsättning. Kostnader och effekter för de närstående är dock vanligen exkluderade från den hälsoekonomiska analysen och det saknas nästan helt rekommendationer över hur de ska inkluderas. I avhandlingen har det föreslagits att ett nytt mått kan användas för att synliggöra och inkludera närståendes effekter i analysen; nämligen R-QALYs. Instrumentet EQ-5D har visat sig kunna fånga delar av närståendes effekter, men det finns troligen andra aspekter som är viktiga för närstående, exempelvis altruistiska preferenser för individens hälsa. Båda direkta och indirekta värderingsmetoder kan användas för att skatta R-QALY-vikter, där de senare kräver närstående-relaterade instrument. Ingen av dessa metoder är dock utan svårigheter och det finns behov av fler studier för att skatta valida R-QALY-vikter. En alternativ metod med stor potential är att använda monetära värderingsmetoder för både närståendes kostnader och effekter.

Det har också visat sig teoretiskt att inkomst kan påverka QALY om individerna beaktar nyttan av konsumtion i sina värderingar. De empiriska testen har dock visat att de flesta inte inkluderar inkomst när de värderar hälsotillstånd. En explicit uppmaning om att beakta inkomst påverkade värderingen av de hälsotillstånd där förmågan att utföra dagliga aktiviteter förändrades. Dessa resultat stödjer därför inkludering av produktionsbortfall i analysen eftersom dessa kostnader inte, eller endast till en låg grad, är inkluderat i individers QALY-vikter. Förlust av fritid är dock redan med i QALY-vikten och detta måste tas hänsyn till för att undvika dubbelräkning.

Om närståendes kostnader och effekter samt kostnaden för individers produktionsbortfall saknas i analysen av behandlingar där dessa delar är av signifikant betydelse kommer resultatet av analysen endast att vara partiellt.

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